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The British
ournal of Surgery

ume 76, Number 1, January 1989

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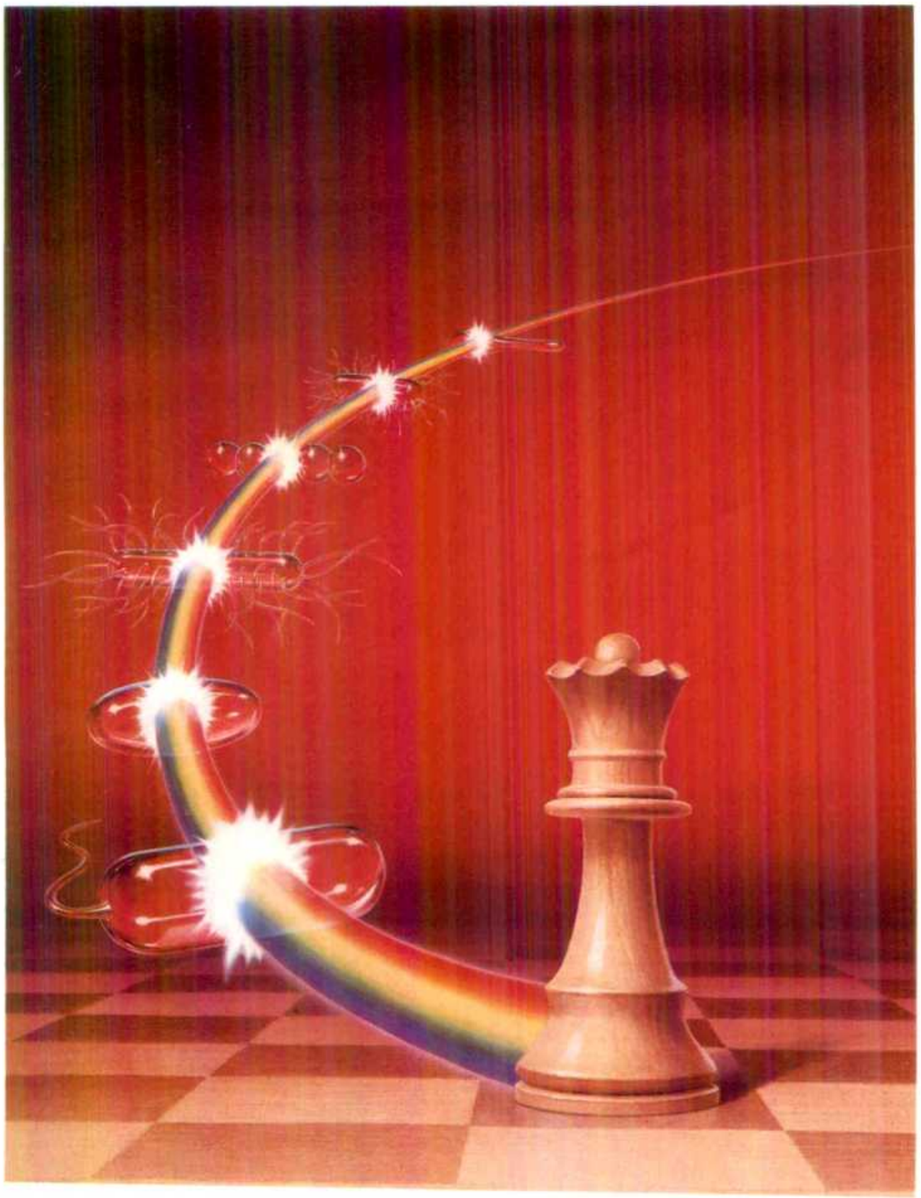
PIPRIL
INTRAMUSCULAR/INTRAVENOUS PIPERACILLIN

Still a key move
in surgical infections



- Proven single agent activity[1-3]
- Broad spectrum cover, including anaerobes.[4] Active against *Strep. faecalis*[5] – unlike cephalosporins, aminoglycosides and metronidazole.
- Highly synergistic with aminoglycosides[6,7]
- Low potential for inducible resistance compared with 'third generation' cephalosporins[8,12]
- Effective concentrations in bile and peritoneal fluid[9,10]
- Well tolerated[11]

Prescribing information. **Indications:** Pipril is a broad spectrum bactericidal penicillin for the treatment and peri-operative prophylaxis of systemic or local infections caused by sensitive organisms. **Dosage:** Adult patients with normal renal function should receive 4-8g daily in divided doses for mild or uncomplicated infections. In serious or life-threatening infections 12-16g daily in divided doses. For peri-operative prophylaxis 2g just prior to surgery followed by at least two doses of 2g at four or six hour intervals. Patients with renal insufficiency may need dosage reduction – see Data Sheet. Children 2 months to 12 years of age: 100-300 mg/kg daily in three to four divided doses. Neonates and infants under two months of age: 100-300 mg/kg daily in two equally divided doses. **Contra-indications:** Penicillin or severe cephalosporin hypersensitivity. **Precautions:** Safety for use in pregnant or lactating women has not yet been established. **Side effects:** Uncommon and typical of injectable penicillins. **Administration:** Pipril is presented as 1g or 2g vials, 4g infusion bottles and 4g infusion packs containing piperacillin as piperacillin sodium. See Data Sheet or package leaflet for full details of preparation and administration. **Product Licence No.** 0095/0073. **Basic NHS Price:** 1g vial £2.98, 2g vial £5.90, 4g infusion bottle £11.66, 4g infusion pack (4g bottle, 50 ml WFI plus needle) £12.43. Further information is available on request.

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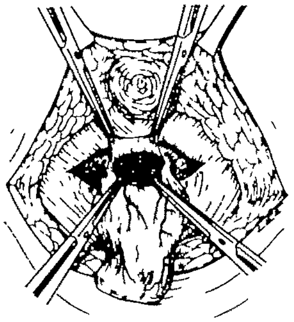

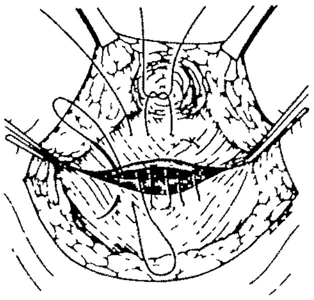

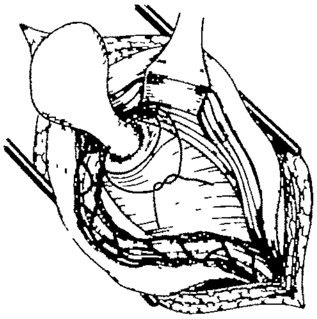

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Br. J. Surg. 1989, Vol. 76, January, 1–2

Surgeons and computers

In the 1980s computers have been characterized not so much by increased cleverness as by shrinking size, increased speed, enormously increased memory and dramatically falling prices. These changes have greatly enlarged the usefulness of computers in medicine and in the business of providing health care. However while surgeons cannot claim to be ignorant of the revolution occurring around them, they have, in general, shown themselves to be uninterested or incapable of exploiting the change. Indeed this journal receives very few papers describing the harnessing of computer power for clinical benefit. It is understandable that surgeons seem to show reluctance in this area; by nature they prefer to deal with diseases that they can see and handle yet nothing could be more covert than the anatomy of computers, nothing more enigmatic than their physiology. Surgeons have no training that helps them to understand these machines and most have had little or no interactive contact with them. The resulting gulf is not entirely the surgeon's fault. The interfaces between computers and humans are too often clumsy and unsympathetic and the exploitation of the computer is too often left to sycophants who can only chatter in jargon.

Early attempts at bringing computers into the area of clinical diagnosis were over-ambitious and, in its non-clinical uses, the computer was and still is perceived largely as a weapon for meddlesome managers. The time must surely have come for surgeons to put away their understandable anxieties and scepticism and instead contribute to relevant and imaginative applications for the new computers. Starts already made include the computerized follow-up of patients, the computer surveying the answers on questionnaires and the results of tests that it has arranged, thus identifying those patients in need of closer clinical scrutiny. In image processing computers may soon be able to provide more than just neater pictures, they will be able to store them digitally and retrieve and transmit them instantly, and so provide a limited interpretive service[1,2]. In the processing and storage of all routine clinical information computers will predominate, and perhaps the mishap of the lost result and the overlooked abnormal result will become a thing of the past. 'Smart cards' the size of credit cards are already capable of holding 20 million bits of information such that patients might carry their own medical records[3]. As the trend to early diagnosis and preventive medicine takes hold, computers will be able to take over some of the mundane questionnaire functions involved.

Even in the difficult area of clinical diagnosis computers have already shown their use, as in the benefits described by Adams *et al.* for a system analysing acute abdominal pain[4]. The application of that system halved the negative laparotomy rate and reduced the mortality rate. Major reservations about the role of computers in diagnosis still exist and are discussed by Sutton in this issue (pp. 82–85). Computers are already central to the anaesthetic and intensive-care monitoring of vital signs and might equally be used to control the administration of drugs and the accurate prescription of drug regimens and parenteral nutrition. The involvement of computers in management already reaches beyond simple audit and data storage to using that data for 'what if...?' exercises in prediction. Surgeons are already prominent in the computerizing of audit but, as in other areas where clinical and managerial functions overlap, certain ideological and philosophical changes will be required if the product of computerized audit is to be used to improve care. Even our concepts of 'clinical freedom' may have to change if audit shows our free practices to be harmful[5]. Where audit points up a need for re-education, the computer will help. Free and easy access to comprehensive medical databases through any hospital computer terminal ought to be normal practice, but the surgeon will only demand such access when he realizes the need and can manipulate the computer. In the not too distant future most medical journals, including this one, will be available through the medium of the computer screen.

Even in his most fiercely protected lair, the operating theatre, the surgeon must expect the computer to intrude. Recent government reports[6,7] have shown that in the UK the average use of available prime weekday theatre time is only 60 per cent. Computers can solve the problem of how to reduce this waste, just as long ago they solved the difficulties of filling the seats on airliners. Within the next few years the new generation of computer-literate young people brought up with computer studies at school and microcomputers at home will be qualifying in medicine. If we are not to

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have two cultures in the surgical team their seniors must be prepared to educate themselves about the general principles of computers. They will not need to be able to type or to understand most of the jargon, but they will need to set aside any phobias they have about screen and keyboard. They will certainly not need to know anything about programming. They will need only to understand the principles, the powers and the limitations of computers and data transmission systems. Readable explanatory books are available[8] but more pragmatic and comprehensible material needs to be produced. In the end, though, all that is needed is an open mind.

A. E. Young

St. Thomas's Hospital
London SE1 7EH
UK

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Br. J. Surg. 1989, Vol. 76, January, 3–4

Lower gastrointestinal bleeding

Over the last decade, there has been a major shift of emphasis with regard to lower gastrointestinal bleeding. The recognition of angiodysplasia as a not uncommon cause of haemorrhage has led us to reassess much of our earlier teaching. In addition to the other common cause of bleeding, namely diverticular disease, acute bleeding may also occur in inflammatory bowel disease, radiation enteritis, and ischaemic colitis, and may originate from vascular tumours. From a clinical viewpoint, bleeding from the distal small bowel, most often from a Meckel's diverticulum, cannot be distiguished from bleeding from the proximal colon.

Angiodysplasia has come to the fore over the last decade as a major cause of gastrointestinal bleeding. In a Hammersmith series of 67 patients with this problem, 13 per cent presented with an initial acute bleed, 46 per cent with recurrent acute bleeding and 33 per cent with chronic bleeding (usually presenting as anaemia). In 7 per cent of patients, angiodysplasia was an incidental finding on angiography and occurred in association with other lesions[1]. Case selection is partly responsible for the fact that angiodysplasia was by far the commonest cause of colonic bleeding seen at the Hammersmith Hospital, being nearly ten times as common as acute diverticular bleeding. It was responsible for 74 per cent of all cases of red bleeding per rectum, 18 per cent of all cases of 'melaena' and 49 per cent of all cases presenting with anaemia secondary to colonic bleeding. Clearly this pattern of disease reflects the experience of the unit to which patients are referred for angiography in the investigation of bleeding, and does not represent the true incidence of angiodysplasia as a cause of bleeding in the population. When diagnosed by angiography, angiodysplasia is almost always in the caecum or ascending colon. Although a higher incidence of angiodysplastic lesions is seen in the left colon at colonscopy, these rarely show on angiography and do not often cause significant bleeding. Angiodysplasia may be diagnosed either endoscopically or by angiography, though the former may be difficult during an acute bleeding episode. However, most such episodes stop spontaneously, so that this is not a practical difficulty.

If angiodysplasia is diagnosed endoscopically then initial treatment should consist of endoscopic coagulation. In some cases this fails and, in occasional patients, angiography demonstrates angiodysplasia which was not visible at endoscopy. In either of these situations, operative treatment may be required. It has become apparent that the presence of angiodysplasia does not necessarily mean that it is the source of bleeding or perhaps the only source of bleeding. Although angiodysplasia is an extremely rare incidental angiographic finding in patients without gastrointestinal bleeding, patients with angiodysplasia frequently have other lesions which are potential sources of haemorrhage. Meckel's diverticulum appears to be particularly common in this context, and jejunal arteriovenous malformations and small bowel tumours have also been found in association. Experience has shown that it is not possible to be certain about the source of haemorrhage when there are two possible sources of bleeding; if such patients come to laparotomy then both potential sources should be dealt with[2].

Bleeding diverticular disease has always been problematic. In the days before angiodysplasia was diagnosed commonly, the mystery remained that diverticular disease was always more extensive in the left colon although it was apparent clinically that bleeding occurred more commonly from the right side. In one series of 100 patients with 144 episodes of bleeding, it was noted that in 58 the bleeding was bright red in colour whereas in 42 it was black and tarry[3]. Left-sided resections were commonly followed by rebleeding, although the disease was more extensive on the left. This led to emphasis being placed on the importance of extensive colectomy when dealing with acute 'diverticular' bleeding, or to the need for a temporary transverse colostomy when deciding which half of the colon contained the source of bleeding before resection. It was noted, however, that bleeding was commoner in patients with extensive diverticular disease than in those where the disease was more localized. In today's context it is very important to question the diagnosis of bleeding diverticular disease. If at all practical, angiography should be employed to determine the site of bleeding. Undoubtedly many patients previously diagnosed as having bleeding diverticular disease were in fact suffering from angiodysplasia. If the patient is losing black tarry stool then angiodysplasia is even more likely, and if a 'blind' resection seems warranted then right hemicolectomy might be the logical choice. For severe red bleeding of unknown origin, subtotal resection of the colon may still occasionally be necessary.

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Where there is serious doubt and the general condition of the patient permits, an alternative option is the creation of a transverse colostomy followed by appropriate colectomy if bleeding recurs. The importance of a full, careful laparotomy, including detailed palpation of the small bowel, cannot be over-emphasized.

Ischaemic colitis rarely causes severe bleeding. When it does, the bleeding is characteristically plum-coloured and is associated with abdominal pain and tenderness. In 10 per cent of cases, ischaemic colitis follows surgery for aortic aneurysm. It can be diagnosed readily endoscopically or by barium enema, and angiography is not necessary.

Radiation-induced colitis commonly presents with bleeding. Radiation is most often given for intrapelvic disease of the female reproductive system or the bladder, and so the most commonly involved parts of the gut are the ileum and the rectosigmoid. In a series of 70 patients with 97 radiation-induced lesions of the gut, 36 involved the rectum and sigmoid[4]. Haemorrhage in such patients may be from a chronic proctocolitis, or may emanate from localized ulceration. Persistent bleeding, or recurrent acute bleeds, may lead to considerable disability. The Edinburgh experience illustrates the usefulness of proctectomy in this situation with excision of the involved rectal mucosa and a coloanal sleeve anastomosis[5]. Although this procedure is not undertaken lightly in such patients, it can bring to an end a cycle of haemorrhage and hospitalization for which no other treatment is effective. The splenic flexure must be brought down for such an anastomosis, as it is free from radiation damage.

J. Spencer

Hammersmith Hospital (Royal Postgraduate Medical School)
London W12 0HS
UK

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Br. J. Surg. 1989, Vol. 76, January, 5–6

Changing patterns in the treatment of rectal cancer

In the last decade, we have seen a technical revolution in the surgical treatment of rectal cancer. The introduction of stapling instruments has allowed the anal sphincter to be conserved in far more patients than previously. Contrary to the views of many Jeremiahs, this revolution has been achieved without an apparent decrease in survival rates or an increase in recurrence rates when compared with the results of abdominoperineal excision of the rectum[1–3]. It is true that selection is important, but there are now few patients who cannot be treated by sphincter-saving resection. The resulting quality of life is far superior to that associated with a permanent colostomy, although frequency of bowel action may still be an inconvenience for some patients with very low anastomoses[4]. However, even this relative imperfection may now be circumvented by the construction of a colonic pouch[5,6].

Despite this creditable performance by surgeons and instrument manufacturers in improving the lot of the patient with rectal cancer, the natural history of the disease has remained unaffected. Over the last 50 years longevity has not improved and, indeed, overall results are depressingly poor. In specialized centres, corrected 5-year survival rates in the last half-century have remained static at around 50 per cent—and this despite an almost 100 per cent increase in operability rates. The national data are likely to be far worse. In the early 1970s, the overall survival rates for rectal cancer in the midlands and in the south-west of the UK was 29 per cent and 23·5 per cent, respectively[7,8], and there is no evidence to suggest that these rates have improved. Another disturbing feature to emerge recently has been the surgeon-to-surgeon variability in local recurrence rates. Phillips and co-workers[9], when reporting the results of the St. Mary's large bowel cancer project, found that the incidence of local recurrence after rectal excision varied from less that 5 per cent to more than 20 per cent, depending on who performed the operation.

Where do we go from here? Have we as surgeons reached the end of the road as regards our ability to influence the natural history of the disease? Should we now accept the sentiments expressed by Sir John Ericksen in 1873: 'There must be a final limit to the development of manipulative surgery. The knife cannot always have fresh fields for conquest, and, although methods of practice may be modified and varied, and even improved to some extent, it must be within a certain limit. That this limit has nearly, if not quite, been reached will appear evident if we reflect on the great achievements of modern operative surgery.'[10]. Ericksen was mistaken in 1873, and, in my opinion, remains so in 1988 with respect to rectal cancer. However, if improvement is to be forthcoming, attitudes have to change and surgeons cannot be complacent. Technique must still play an important part in preventing recurrence; why else should there be so much surgeon-to-surgeon variation? It is true that some of these differences may be due to demographic differences, but they seem more likely to be due to variations in the extent of local tissue removal. We now know that the mesorectum and pararectal tissues frequently contain microscopic tumour deposits resulting from radial spread of the tumour[11]. Not only are such deposits not suspected by the surgeon at operation or by the pathologist on routine examination of the specimen but if left *in situ* they seem to be the main cause of local recurrence. Surprisingly also, abdominoperineal excision as performed by many surgeons is no more effective in eradicating this form of spread than sphincter-saving resection. It would seem prudent, therefore, that no matter which type of operation is performed, the whole of the mesorectum should be excised[12]. However, no matter how aggressive the surgeon is in dealing with this form of spread, it is unlikely that he will be able to remove it all. Clearly, some form of local adjuvant therapy is required. In our present state of knowledge, radiotherapy seems the most logical choice. It is of particular interest that, while many adjuvant radiotherapy trials have failed to show any overall improvement in recurrence rates, patients with fixed or partially fixed tumours seem to have benefited from even quite low doses of radiation[13]. As these patients are in the main those with macroscopic spread, one can only speculate on how effective the same treatment would be if it was directed at microscopic disease. Such a policy would necessitate an enormous increase in the workload of our pathologist colleagues, but would be justified if it proved to be beneficial. A controlled randomized trial is urgently required.

However, it must be accepted that even if such treatment reduces the incidence of local recurrence, it is unlikely to improve survival rates. To date, few trials of adjuvant

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radiotherapy (when given without chemotherapy) have been shown to prolong life, even if local recurrence rates have been reduced. Presumably, this reflects the fact that distant spread has occurred before or after local treatment has started. We know that approximately 30 per cent of patients with colorectal cancer have occult metastases at the time of surgery, and these cannot be detected by conventional scanning techniques[14]. Systemic adjuvant chemotherapy seems appropriate. It is of interest to note that in a recent large trial of adjuvant therapy in rectal cancer[15], the group of patients who received a combination of radiotherapy and systemic 5-fluorouracil and semustine was the only one to show a significant improvement in survival. This was not, however, achieved without significant morbidity. Such results suggest that this type of therapy is effective, but should be employed only for high-risk groups. This conclusion highlights the need for appropriate assessment and staging. We urgently require a means of detecting microscopic distant spread and perhaps the hepatic perfusion index will be the answer[16]. Even if it is not, a standardized method of assessment which takes into account the clinical and pathological characteristics of the disease needs to be established. Such a system might help to detect the high-risk groups, and it should also detect patients whose prognosis is so hopeless that they might be best treated by a local procedure as opposed to a more major resection. Such a system has recently been proposed[17] and it is to be hoped that these recommendations will be generally accepted.

The other great hope for improving the results of treatment is early detection of the tumour. We all await with interest the results of current controlled trials of faecal occult blood screening[18]. However, regardless of the outcome, surgeons will still be dealing with established and often advanced disease for a long time to come. If we are to make any impact on the eventual outcome, we must have a more uniform approach towards the disease, eliminate surgeon-to-surgeon variability in our results and be more prepared to enter our patients into adjuvant trials. Our considerable achievements in preserving continence must be matched by a concerted effort to improve survival and recurrence rates.

N. S. Williams

The London Hospital
London E1 1BB
UK

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Choice of material for above-knee femoropopliteal bypass graft

J. A. Michaels

Department of Surgery, University College and Middlesex School of Medicine, London, UK
Correspondence to:
Mr J A. Michaels, Department of Surgery, The Rayne Institute,
5 University Street,
London WC1E 6JJ, UK

Autogenous saphenous vein is generally considered to be the best material for arterial bypass grafts below the inguinal ligament. Recent results have suggested that the advantage of vein over prosthesis is more pronounced in a distal situation, but it is not immediately apparent whether the difference is sufficient to justify a policy of using prosthesis for the initial above-knee graft to preserve the vein in case later surgery is required. An attempt has been made to answer this question. The literature has been reviewed to obtain estimates of the patency rates for grafts in different situations and a mathematical model has been set up using these figures to predict the outcome of different treatment policies. The model can be used to predict the result of alteration or inaccuracy in the data or to make use of the results of newly reported studies. The model predicts that the use of prosthesis for an initial graft will reduce the overall patency and substantially increase the requirement for reoperation, even if the present data give a substantial overestimate of the advantages of vein above the knee.

Keywords: Arterial occlusive disease, vascular graft patency, vascular prosthesis, saphenous vein, vascular surgery, models, theoretical

For the past three decades there has been a steady expansion of the available methods for the relief of symptoms due to vascular occlusion. Bypass grafting has become an established method, with autogenous vein being the usual preferred material where a vein of suitable size is available[1]. In other situations there is a variety of prosthetic materials to choose from. New materials have been introduced and shown to be satisfactory for replacement of large calibre vessels such as the aorto-iliac arteries, but it is generally accepted that autogenous vein is better than a prosthesis in the case of arterial disease distal to the inguinal ligament[2]. Recently, however, there have been many series of patients in whom some of the newer materials have been used in this situation with reasonable results. The results, as would be expected, seem to be at their best in situations of high flow and correspondingly low risk. In particular, some studies have failed to show a significant advantage for vein when used for above-knee femoropopliteal bypass[3,4]. This has led several authors to suggest that synthetic materials should be used as first choice in these situations and the vein preserved for later coronary or distal grafting, where the advantages of vein are well established[5–7].

To establish whether such a policy can be justified on the present evidence certain questions need to be answered. Does the existing evidence give an indication of differences in patency rates between vein and prosthesis when used above the knee? If there is such a difference, are there arguments in favour of preservation of the vein? Finally, are the potential benefits sufficient to outweigh any possible disadvantages?

Published evidence

Many published studies describe the results of using various types of peripheral vascular grafts in different situations. Unfortunately there are difficulties in attempting to compare the results of different series[8]. There are many materials and surgical techniques and there are a multitude of known and putative risk factors, the incidence of which varies from one series to the next. There is a paucity of controlled randomized trials, most studies using historical or non-randomized concurrent controls, and not all trials use the same definitions in describing symptoms and results[9]. Bearing these reservations in mind, the present evidence has been reviewed (*Tables 1–4*). The studies quoted in the tables are limited to those published over the past 10 years as development of surgical techniques, changes in indications for surgery and new graft materials make comparisons with earlier results of doubtful value. The studies quoted are also limited to those in which the results could be extracted separately for groups of patients almost completely composed of those having either prosthetic or vein graft above or below the knee. Papers were located by a computerized literature search followed by a manual search of the major

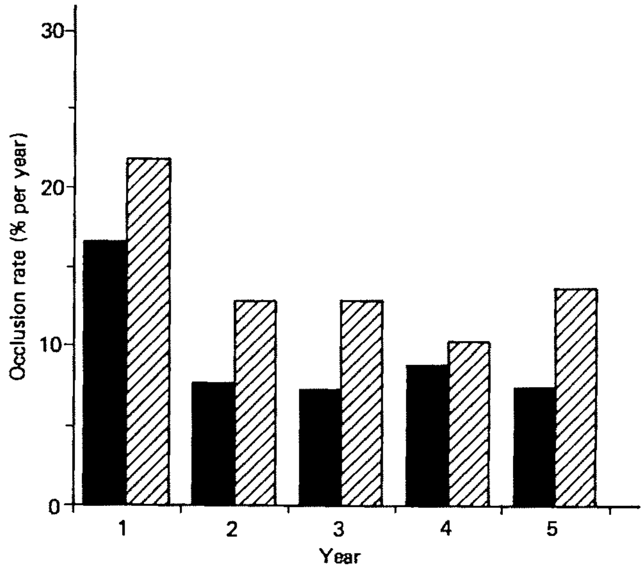

Figure 1 *Occlusion rate for above-knee grafts for each year after surgery. ■, Vein grafts; ■, prosthetic grafts*

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Table 1 *Review of literature on above-knee vein grafts*

Author	Year	No	Occlusions (%) Year 1	Occlusions (%) Year 2+	Claudicants (%)
Brewster *et al.*[10]	1983	85	15	4	20
Cranley and Hafner[11]	1981	219	17	6	100
Cranley and Hafner[11]	1981	168	30	4	0
Naji *et al*[12]*	1978	100	33	9	30
Rafferty *et al*	1987	57	21	7	28
Rosenthal *et al.*[14]	1983	20	8	6	60
Simone *et al.*[15]	1981	26	15	0	35
Sterpetti *et al.*[7]	1985	17	0	15	
Szilagyi *et al.*[16]	1979	35	25	5	34
Taylor *et al*[17]	1986	45	8	7	33
Veith *et al*[18]	1986	85	15	10	11
Yashar *et al*	1981	24	8	8	50
Total number of patients			881		
Average occlusions year 1(%)			20·2		
Average occlusions years 2–5 (%) (Weighted for number of patients)			6·2		
Equivalent 5-year patency (%)			61·8		

* Includes a small number of below-knee grafts

surgical journals. This identified over 120 reported series of femoropopliteal grafts of which approximately one-third contained sufficient detail for them to be included.

The results reported here confirm that there is a considerable difference in long-term patency between vein and prosthetic material, more pronounced in the below-knee site. Most of these trials confirm the tendency for there to be a high initial failure rate, with a slower, almost constant attrition rate over subsequent years (*Figure 1*). For this reason the results have been presented as rates of occlusion in the first year and an average for subsequent years. This allows for the pooling of more data from studies in which the results are presented after differing time periods.

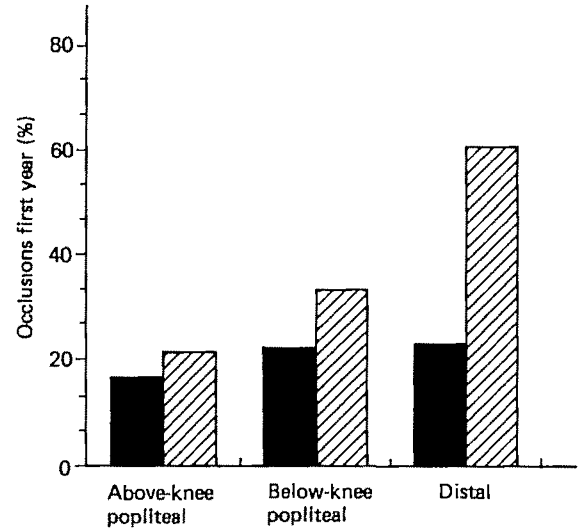

Figure 2 *Occlusion rate in first year* versus *anastomotic site for vein and prosthetic grafts.* ■, *Vein grafts*; ■, *prosthetic grafts*

Several factors which may influence the results of surgery vary between groups. The site of the distal anastomosis in below-knee grafts is a possible risk factor (*Figure 2*) with distal grafts having a worse prognosis especially when using prostheses. Opinions vary about the relative merits of different prosthetic materials[41,42] but it seems to make little difference overall (*Figure 3*) except that polytetrafluoroethylene (PTFE) has better reported results than Dacron below the knee but not as good above the knee. A possible explanation for this lies in the differences in mechanical properties which may make Dacron more suitable in situations where it is not necessary to cross a

Table 2 *Review of literature on above-knee prosthetic grafts*

Author	Year	No.	Occlusions (%) Year 1	Occlusions (%) Year 2+	Material	Claudicants (%)
Brewster *et al.*[10]	1983	75	15	14		20
Charlesworth *et al.*[19]	1985	53	30	13	PTFE	25
Christenson *et al*[20]	1985	153	16	3	PTFE	20
Cranley and Hafner[11]	1981	73	15	8	PTFE/HUV	100
Cranley and Hafner[11]	1981	100	45	12	PTFE/HUV	0
Evans *et al*[21]	1981	73	30	25	PTFE	47
Haimov *et al*[5]	1979	59	23		PTFE	37
Hallett *et al.*[22]	1981	28	15	14	PTFE	10
Kenney *et al.*[23]	1982	155	15	9	Dacron	58
Mosley *et al.*[24]	1986	37	22	16	Dacron	33
Quinones-Baldrich *et al.*[6]	1984	45	15	5	PTFE	33
Rafferty *et al*[13]	1987	106	21	19	PTFE	40
Raithel *et al.*[25]	1980	87	10		PTFE	33
Rosen *et al*[3]	1986	75	18	11	PTFE/HUV	
Rosenthal *et al.*[14]	1983	25	10	10	PTFE	36
Rosenthal *et al*[14]	1983	25	15	9	Dacron	32
Simone *et al.*[15]	1981	55	30	20	PTFE	35
Simone *et al*[15]	1981	33	35	15	Dacron	
Sladen and Maxwell[26]	1981	14	36		PTFE	46
Sterpetti *et al.*[7]	1985	90	22	9	PTFE	46
Veith *et al.*[18]	1986	91	18	23	PTFE	10
Williams *et al.*[27]	1985	118	60	23	PTFE	10
Yashar *et al*[4]	1981	45	8	8	Dacron	50
Total number of patients	1615					
Average occlusions year 1 (%)	23·5					
Average occlusions years 2–5 (%) (Weighted for number of patients)	13·3					
Equivalent 5-year patency (%)	43·2					

PTFE, polytetrafluoroethylene, HUV, human umbilical vein. Dacron® is a registered trademark of E I. Du Pont de Nemour Incorporated

Table 3 *Review of literature on below-knee vein grafts*

Author	Year	No	Occlusions (%) Year 1	Occlusions (%) Year 2+	Site	Claudicants (%)
Barry *et al.*[28]	1985	50	20	8	Popliteal	20
Brewster *et al.*[10]	1983	262	15	5		20
Buchbinder et al [29]	1986	74	10		Distal	16
Burnham *et al* [30]	1978	39	44		Popliteal	27
Bush *et al.*[31]	1985	81	18	3		0
Cranley *et al.*[11]	1981	29	32	15	Distal	10
Edwards *et al* [32]	1980	59	18		Distal	10
Hobson *et al* [33]	1980	46	35	17		0
Rafferty *et al.*[13]	1987	170	14	5	Popliteal	29
Rafferty *et al.*[13]	1987	98	37	18	Distal	0
Reichle *et al.*[34]	1980	164	44	4		5
Rosen *et al.*[3]	1986	59	25	12	Popliteal	
Sidawy *et al.*[35]	1986	78	28	0	Distal	6
Szilagyi *et al.*[16]	1979	429	30	5	Popliteal	30
Taylor *et al.*[17]	1986	118	13	3	Popliteal	33
Taylor *et al.*[17]	1986	76	8	5	Distal	33
Veith *et al* [18]	1986	62	15	4	Popliteal	8
Veith *et al* [18]	1986	106	35	9	Distal	8
Yashar *et al.*[4]	1981	46	9	9		50
Yeager *et al* [36]	1982	36	22	6	Popliteal	0
Yeager *et al* [36]	1982	34	35	11	Distal	0
Total number of patients		2116				
Average occlusions year 1 (%)		24·3				
Average occlusions years 2–5 (%) (Weighted for number of patients)		6·3				
Equivalent 5-year patency (%)		68·4				

Table 4 *Review of literature on below-knee prosthetic grafts*

Author	Year	No.	Occlusions (%) Year 1	Occlusions (%) Year 2+	Material	Site	Claudicants (%)
Brewster *et al* [10]	1983	133	50	13			20
Burnham *et al.*[30]	1978	47	35		PTFE		17
Charlesworth *et al* [19]	1985	81	50	20	PTFE		25
Christenson *et al.*[20]	1985	74	44	7	PTFE	Popliteal	20
Christenson *et al* [20]	1985	54	44	3	PTFE	Distal	20
Clyne *et al.*[37]	1979	20	40	33	PTFE	Popliteal	40
Cranley *et al.*[11]	1981	29	52	25	PTFE/HUV		10
Dardik *et al.*[38]	1982	169	43	13	HUV	Distal	10
Dardik *et al* [38]*	1982	286	18	10	HUV	Popliteal	10
Edwards and Mulherin[32]	1980	29	76		PTFE	Distal	10
Edwards and Mulherin[32]	1980	15	90		HUV	Distal	10
Evans *et al* [21]	1981	25	35	8	PTFE	Popliteal	47
Gupta *et al* [39]	1980	83	10	10	PTFE	Popliteal	0
Haimov *et al* [5]	1979	125	29	21	PTFE	Popliteal	63
Hallett *et al.*[22]	1981	54	40	25	PTFE	Popliteal	10
Harris *et al.*[40]	1984	60	65	60	HUV	Popliteal	8
Hobson *et al.*[33]	1980	46	66		Dacron		0
Mosley *et al* [24]	1986	29	48		Dacron	Popliteal	33
Quinones-Baldrich *et al* [6]	1984	15	20	20	PTFE		33
Rafferty *et al* [13]	1987	120	50	18	PTFE	Popliteal	10
Rafferty *et al* [13]	1987	76	69	18	PTFE	Distal	10
Raithel and Groith[25]	1980	81	15		PTFE	Popliteal	33
Sladen and Maxwell[26]	1981	85	46	25	PTFE	Popliteal	46
Veith *et al* [18]	1986	80	16	9	PTFE	Popliteal	10
Veith *et al* [18]	1986	98	50	60	PTFE	Distal	10
Yeager *et al* [36]	1982	33	30	14	PTFE	Popliteal	0
Yeager *et al* [36]	1982	30	40	40	PTFE	Distal	0
Total number of patients		1977					
Average occlusions year 1 (%)		39·0					
Average occlusions years 2–5 (%) (Weighted for number of patients)		18·7					
Equivalent 5 year patency (%)		26·6					

* Includes a small number of above-knee grafts. PTFE, polytetrafluoroethylene, HUV, human umbilical vein

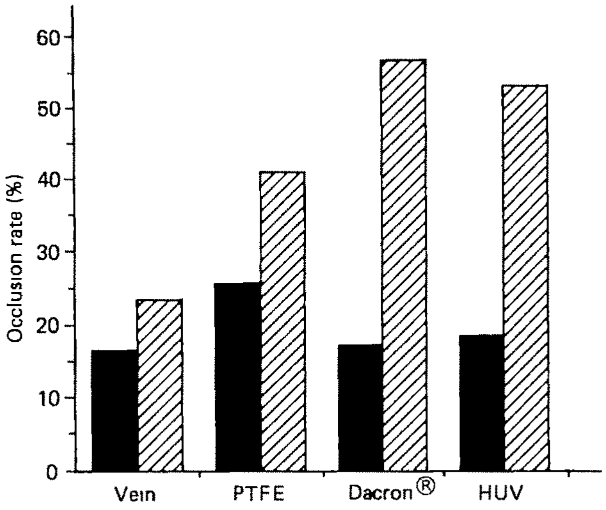

Figure 3 *Occlusion rate in first year for various graft materials in above- and below-knee situations PTFE, polytetrafluoroethylene, HUV, human umbilical vein.* ▨*, Above-knee,* ■*, below-knee*

joint[43]. Individual studies have shown that operations for salvage fare worse than those for claudication[16] but there is no good correlation in the overall trend.

Evidence in most situations suggests that vein is better than prosthetic material for long-term patency This is seen to be most marked in situations where there is known to be a high risk of failure. In the coronary circulation the vein is considered far preferable to any prosthesis[44]. In peripheral disease the factors which indicate high risk of re-occlusion—such as poor run off[45,46], critical ischaemia[45–47], distal grafting[46,48,49] and continued smoking[48,50]—all seem to accentuate the disadvantages of using a prosthetic graft. In none of the studies reviewed does any prosthesis have superior results to vein in any situation. In the case of above-knee grafts there seems to be little difference in the first-year results but a much higher attrition rate for the prosthetic grafts in subsequent years. This is particularly important as the follow-up is sometimes incomplete and is made more difficult by the death rate in patients with femoropopliteal atherosclerosis[16]. In those studies in which it was specified, the average yearly mortality rate was approximately 10 per cent, giving an overall 5-year survival of about 59 per cent.

The problem of inadequate follow-up is well demonstrated in several trials in which the authors have come to the conclusion that there is no significant advantage in the use of vein[6,14,17]. Of these trials the largest 5-year follow-up in the vein graft group is based on 24 patients. In this situation, type II statistical errors become a problem with a <50 per cent chance of showing a statistical difference between the groups even if the true difference in 5-year patency is >25 per cent Added to this is the further problem that none of these trials is randomized, therefore doubts must exist about the comparability of the treatment groups

One randomized controlled trial of a reasonable size has been reported by Bergan *et al.*[51] and Veith *et al.*[18]. In this trial 845 infra-inguinal bypasses were performed with randomization to autologous saphenous vein or PTFE. The results obtained broadly follow those suggested by the accumulated data reported above For most groups a statistically significant advantage for autologous vein is shown. Again, however, the advantage shown for vein in the above-knee situation (61 per cent *versus* 38 per cent patency at 4 years) is not statistically significant due to the very small number of patients who could be followed for this length of time, even in this very large and prolonged multicentre trial. There are other problems in the interpretation of this trial, particularly regarding the randomization procedure Patients were randomized before investigating whether there was an adequate vein for bypass, and this was only established at the time of surgery in those patients who were allocated vein grafts. This led to a large number of patients being excluded from the vein graft group and forming an 'obligatory PTFE' group. When the results were analysed this group fared significantly worse than the randomized PTFE group. This suggests that either there was some unintentional selection taking place or that vein quality is an indicator of the likelihood of prosthetic graft failure.

In order to use accurate estimates for further modelling it would be desirable to combine the results of all the reported studies to obtain patency rates and confidence limits for the combined data. Statistical methods for doing this, termed 'meta-analyses', have been described and discussed in the medical literature[52,53] Several problems are encountered in trying to apply these techniques to the present study. Many of the reviewed papers present inadequate data for the results of different materials in different situations to be individually assessed, most of the reported studies are uncontrolled, and where there are controls these are usually non-randomized Using the few controlled trials of above-knee grafts that have sufficient data[4,10,11,13–15,18] the homogeneity was assessed graphically as described by L'Abbé *et al.*[52] (*Figure 4*). The results appear consistent and the two series with <25 per cent risk reduction have a high proportion of claudicants[4], or are a subgroup composed only of claudicants[11].

Taking these few studies and analysing the combined data for prosthesis against vein graft above the knee using the Mantel–Haenszel statistic[54] gave a result significant at the 0·05 level after the first year and figures significant at the 0·01 level after 2 and 3 years. It must be noted that these results are based on only a small group of studies from which some of the data had to be calculated and sometimes extracted from graphical presentations as the raw data were rarely published.

Overall, there seems to be close agreement between the one sizeable randomized trial and the figures for both the unrandomized controlled studies and the collected uncontrolled data. However, these points do not exclude the possibility of a selection bias common to all the trials, or a reporting bias.

Despite reservations about the quality of the data the figures presented are the best estimate that is currently available and, until much larger randomized trials are reported, this is the information on which clinical decisions must be based. It can be seen that the vein graft has the best reported patency in all situations The question remains about whether there is any potential advantage in using prosthetic material rather than vein that would justify its preferential usage.

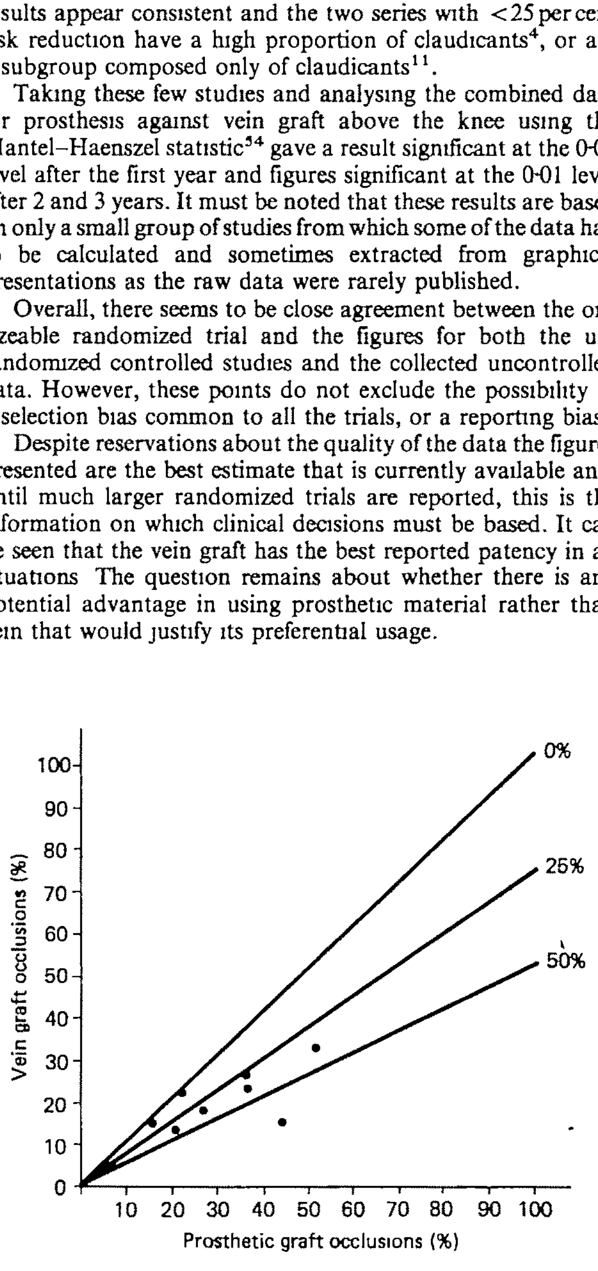

Figure 4 *Homogeneity of controlled trials of femoropopliteal grafts above the knee at 2 years Lines represent 0, 25 per cent and 50 per cent reduction in hazard rate for vein compared with prosthetic grafts*

Two main arguments have been put forward. Firstly, that the operation is faster with fewer complications and, secondly, that it is desirable to preserve the vein in case it is required later for coronary or distal bypass where the advantages of its use are more marked.

Although it is generally agreed that the operation using a prosthesis is quicker, the case for corresponding reduction in mortality and morbidity has not been shown by any of the trials referred to above, and does not necessarily follow because of the potential for increased morbidity due to the introduction of a prosthesis and the associated increase in risk of infection[20,55].

The question of vein preservation for coronary surgery does not stand up to close scrutiny. Firstly, it could only, logically, be applied to operations on the second leg, and only a minority of patients has surgery to both legs[56] Secondly, although it is well established that ischaemic heart disease is a major cause of mortality after peripheral vascular surgery, the number of patients who come to cardiac surgery is small[57], perhaps partly because restraints on resources in this country make the operation uncommon in the age group that undergoes peripheral vascular surgery. Also, the availability of satisfactory alternatives such as the internal mammary artery and the short saphenous and arm veins, means that the lack of a saphenous vein due to prior use for limb revascularization is unlikely to be encountered as a major problem.

The remaining question is whether the advantages, which have been shown for the use of the vein in the below-knee situation (*Tables 3–4*), are sufficient to justify its preservation at the time of original surgery in case later salvage surgery is required.

Mathematical modelling

In order to attempt to answer this question a mathematical model has been set up using a computer spreadsheet to study the results of various treatment policies on the overall patency and number of operations required. This is carried out by considering a time interval and determining from the available data what proportion of patients are expected to be subject to various events, such as graft failure, salvage surgery or death The number of patients remaining at risk at the end of the period can then be calculated and the process repeated for the next period. In this way the overall results in terms of the proportion of patients requiring revision of their grafts, and those with patent and occluded grafts, can be estimated from the published data. By assuming different treatment policies and entering different basic data, new sets of results can be repeatedly generated to model a different set of circumstances.

For this to be done certain assumptions and simplifications are made:

1. The occlusion rate for each type of graft is presented as an occlusion rate for the first year and an average rate per year for subsequent years. As discussed above this produces a close approximation to the published data and allows the pooling of a larger number of studies
2. Mortality is taken as two components, a figure for operative mortality and an average yearly figure for overall mortality. Operative mortality for the initial above-knee operation is about 5 per cent and has not been shown to depend on graft material. For subsequent salvage procedures the operative mortality has been taken as 5 per cent which is an average of several reported figures for this type of operation[30,58–62] For the average yearly mortality a rate of 10 per cent has been obtained from a survey of several papers[13,56,62–64], which, as stated above, is equivalent to a cumulative survival of about 59 per cent at 5 years.
3. A further figure which is required for the model is the proportion of graft occlusions which lead to the need for further surgery. It is known that many grafts occlude without symptoms or with symptoms that are not sufficient to warrant further intervention[8] For the model it has been assumed that all patients with occluded above-knee grafts whose condition deteriorates would require further surgery, that this would always be a below-knee procedure and that no patient would have amputation without an attempt at salvage surgery. Since those patients without an adequate vein do not have a choice of initial treatment, it is assumed that those in whom the vein was used at the initial operation would have to have a prosthetic graft and that the others would all have a vein available for the salvage procedure. The evidence from several studies is that the proportion of occlusions which require further surgery on these criteria is about 50 per cent[65] although there are some differences between those in whom the initial operation was for claudication and those in whom it was for critical ischaemia[66,67].
4. The model only takes account of second operations for limb salvage. The possibility of third and subsequent attempts at limb salvage is ignored. There is little evidence that these play a significant part in the overall results, and in any case the vein would no longer be available and so the subsequent course is independent of initial treatment.
5. The model assumes that mortality and graft occlusion are independent apart from the operative deaths This is probably largely true as the major causes of mortality in this group of patients are ischaemic heart disease and cerebrovascular disease, and peripheral vascular disease is only implicated as a cause of death in a small number of cases[56].

Having constructed the model with these constraints the appropriate figures have been extracted from the reviewed literature as described above. The results are shown in graphical form in *Figure 5*. They show a clear overall advantage in using the vein in the initial graft, while the alternative increases the number of additional operations and also causes a lower 5-year patency when considering both first and second grafts. There is also a slight increase in mortality owing to the operative mortality associated with the larger number of salvage procedures.

It is clear that these figures are based mainly on non-randomized trials and so the original data are open to question. However, if one looks at the overall results from both collected published data and the large randomized trial referred to above then it is suggested that the advantage of using vein in the above-knee situation is an improvement of approximately 40–60 per cent in the expected 5-year patency rate. Even if this is an over-estimate and the real difference is only half this then the results of the model still hold.

It is worth looking at some of the implications of this. Using the method described by Remington and Schork*[68] for estimation of sample size and assuming there is actually a 20 per cent difference in 5-year patency, the number of grafts required at 5 years in order to have a 95 per cent chance of showing significance ($P < 0.05$) is about 160 in each of 2 randomized groups Because of the high mortality and loss from trials, and the fairly small proportion of patients who would be suitable for initial randomization, it would require an extremely large group of patients to have a good change of this level of follow up. It is of note that none of the trials reported to date has managed to accumulate 5-year follow up on even half this number of patients

There is a difference in the outlook for certain subgroups, for example those with good or poor run off, smokers and non-smokers, diabetics and non-diabetics, or those with claudication or critical ischaemia It would therefore be desirable to study these groups separately with a resulting multiplication in the number of subjects required

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* *There are methods available for the estimation of sample size in life table analyses but these require assumptions about the nature of the hazard function and, because of the high level of censoring of data expected in this kind of trial, these estimates differ little from those provided by the method used*

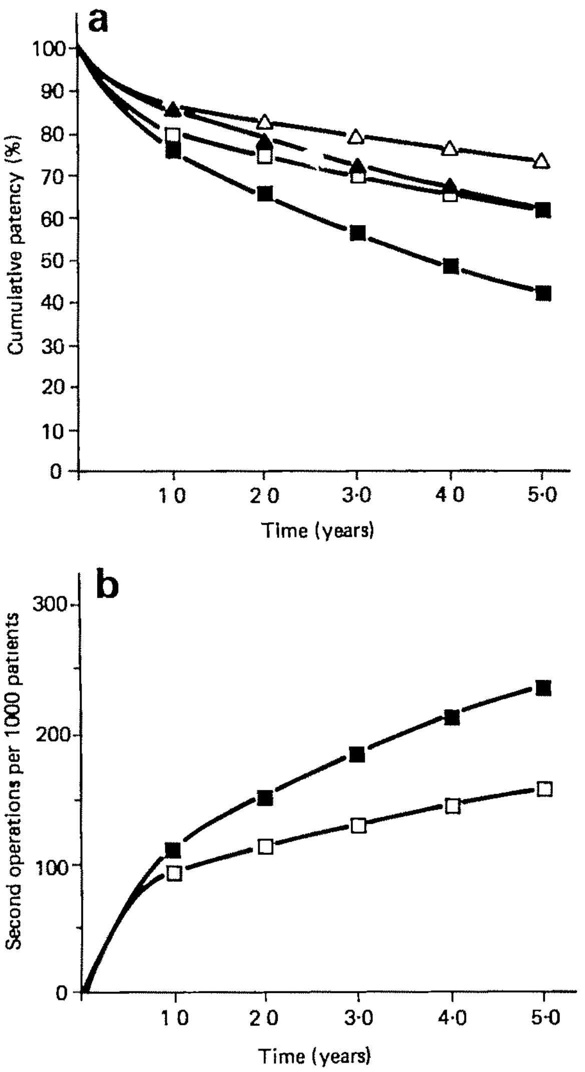

Figure 5 *Results of model comparing vein with prosthesis as an initial above-knee graft* **a** *Patency of initial graft and patency including reoperations* □, *Vein first primary patency;* △, *vein first total patency;* ■, *prosthesis first primary patency,* ▲, *prosthesis first, total patency.* **b** *Number requiring second operations* □, *vein graft first,* ■, *prosthetic graft first*

As mentioned before there seems to be a trend towards more marked differences in patency between vein and prosthesis when the chances of failure are higher. However, this may be partly due to a statistical problem in that it is far more difficult to show a difference in the incidence of an event if there is a low event rate For example, assuming that the 5-year patency for vein grafts was 60 per cent and a prosthesis was 50 per cent more likely to occlude in a given set of circumstances, it would require about 160 patients in each group to have a 95 per cent chance of showing the difference. However, to show the same percentage increase in occlusions in a lower risk group, with an 80 per cent 5-year patency for the vein graft, would require more than twice as many patients This point is demonstrated graphically by Friedman *et al.*[69].

Discussion

All the evidence reviewed suggests an advantage in using vein for above-knee bypass grafting. If there is really no difference in the results then it would be surprising that not one of these trials suggests, purely by chance, that any prosthetic graft is better than vein As has been seen above there is considerable difficulty in designing a trial which would have sufficient 'power' to have a good chance of showing a difference of the order of 10–20 per cent in 5-year patency in a subgroup of patients with infra-inguinal disease. However, the mathematical modelling confirms that even a small difference in 5-year patency could not be compensated for by the advantages of saving the vein for later salvage procedures and no other reasonable argument has been substantiated for the preferential use of a prosthesis.

A different approach to this problem is to look at a situation in which it is more likely that a difference will exist. For example, it is established that the 'quality' of the vein as judged by the operating surgeon is an indicator of its likely long-term patency[16]. Despite this, different series show widely differing rates of vein usage[24,33,70–73] so it would seem reasonable to undertake a prospective trial in which the poorer quality veins are compared with a prosthesis.

Another area which requires further study is that of improving the results for distal bypass when the vein is not available. Recent papers reporting promising results when using jump grafts[74,75], composite grafts[76–78] and alternative veins[79–81] may offer some hope in this respect

Perhaps one of the most important conclusions that arises from a review of the literature is a recognition of the statistical problems of drawing conclusions from insufficient data. This has been demonstrated by Frieman *et al*[82], who found in a review of 71 clinical trials that most had a high chance of missing a difference in result that would be considered to be clinically relevant. This is just as common in other areas of research[83] and in this case it is unfortunate that so many conclusions have been drawn based on data that are not sufficient to exclude a sizeable difference in 5-year patency.

It may be that with developments in graft materials, further controlled trials will identify a group of patients in which an initial prosthetic graft has an advantage. However, on the present evidence, the overall conclusion must be support for the traditional view that autogenous saphenous vein remains the graft material of first choice for all infra-inguinal bypass surgery.

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Announcement

With effect from the February issue of the British Journal of Surgery, the Editors are pleased to announce that the contents list of the journal *Surgery* will be published monthly at the end of each issue.

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Complications of intravenous feeding catheters

M. M. Mughal

University Department of Surgery,
Manchester Royal Infirmary,
Manchester, UK
Correspondence to:
Mr M. M. Mughal, Royal Preston
Hospital, Sharoe Green Lane,
Fulwood, Preston PR2 4HT, UK

Complications of intravenous nutrition are uncommon but may prove problematic in patients requiring long-term nutritional support. This article reviews the complications associated with intravenous catheters with particular emphasis on problems associated with insertion, catheter-related sepsis, venous thrombosis, catheter occlusion, endocarditis and intracardiac thrombus formation.

Keywords: Intravenous feeding, sepsis, complications

Parenteral nutrition is widely used to support the treatment of patients with severe sepsis, trauma and gastrointestinal malignancy, and home parenteral nutrition has an established place in the treatment of intestinal failure. Of the many advances which have made long-term parenteral nutrition feasible, the development of the Silastic® (Dow Corning, Reading, UK) catheter[1] has been arguably the most important, enabling safe, reliable central venous access.

Complications of parenteral nutrition are uncommon but may pose considerable problems of management in those requiring long-term nutritional support. Outside specialist centres, catheter sepsis remains the most common complication, resulting in a considerable morbidity and frequently leading to the premature termination of treatment. Yet compared with many other aspects of parenteral nutrition little has been written about the potential for, and the morbidity of, catheter-related complications.

Improvements in the design and care of catheters have considerably reduced the incidence of infection, occlusion and mechanical failure but cases of symptomatic central venous thrombosis are being reported in ever-increasing numbers[2–5]. The most extreme form of this complication, occlusion of the vena cava, poses great difficulties in re-establishing central venous access and may be further complicated by a number of potentially fatal complications such as pulmonary embolism. Although it is unlikely that the actual incidence of central venous thrombosis is rising, greater awareness and the increasingly widespread use of parenteral nutrition are bound to increase its prevalence. A further serious problem is that of intracardiac thrombus formation, a complication which has only recently been recognized[6–10].

The object of this paper is to review the incidence, aetiology and management of catheter-related complications with emphasis on prevention.

Complications of insertion

Complications directly attributable to catheter insertion occur in 3–12 per cent of cases[2,11–13]. Virtually any structure in the vicinity of the vein being catheterized can be injured but the most frequent injuries, reflecting the popularity of the percutaneous infraclavicular approach to the subclavian vein, are to the pleura or subclavian artery. A significant pneumothorax requires a chest drain but a mediastinal haematoma is often self-limiting and does not usually require specific treatment.

Catheter embolism is rare now that the dangers of inserting plastic catheters through metal needles are widely recognized. Should it occur, the embolus usually can be recovered by a radiologist experienced in interventional methods[14]. Air embolism may occur during insertion from faulty technique, but it is more commonly due to the accidental disconnection of the drip tubing[15], a complication that can be avoided by using Luer-lock connections.

Certain complications presenting many hours or even days after a seemingly straightforward procedure may also be attributable to insertion. For instance, rupture of the innominate vein[16] and hydrothorax have been reported days after satisfactory use of an easily inserted catheter. The exact mechanism of such a presentation is unclear but rupture of the vein has been attributed to the repeated movement of an incorrectly positioned catheter tip against the vein wall, especially when using stiff catheters[17]. However, 'osmotic' injury from hyperosmolar solutions may also be a factor[18]. Rare complications include perforation of the chambers of the heart[19–22], pulmonary artery[23] and inferior vena cava[24] with or without cardiac tamponade. One of the most bizzare complications reported is paraplegia due to infusion into the spinal canal[25].

Catheterization by cut-down has been advocated by some on the basis that it is safer than percutaneous insertion. Exposure and catheterization of the superficial veins (the basilic at the elbow, the cephalic below the clavicle, the external jugular and the saphenous) is relatively simple and safe. However, the advantages of catheterization under direct vision may be outweighed by the potential complications of exposing major veins such as the axillary or the internal jugular in the hands of those without special expertise. In fact, in experienced hands both percutaneous catheterization and cut-down have a low and comparable morbidity[26,27]. In most cases it should be possible to insert a catheter either by percutaneous puncture or cut-down onto a superficial vein. Formal exposure of major veins, which may require general anaesthesia, should now only be necessary for inserting especially large calibre catheters and when percutaneous puncture is considered hazardous (as in those with a bleeding tendency) or has failed. Using vessel dilators and peel-apart sheaths even large calibre, cuffed catheters can now be inserted percutaneously by the Seldinger technique.

Complications can be kept to a minimum by careful attention to technique and concentrating experience in the hands of a few interested individuals. The best time to correct errors is during the procedure and the operator should satisfy himself that the catheter is correctly sited by ensuring that blood can be freely aspirated through it and by checking its position by X-ray. An image intensifier considerably simplifies positioning by allowing one to see the effects of catheter manipulation on the position of its tip.

Catheter-related sepsis

The incidence of catheter-related sepsis varies between 2·8 and 14 per cent[12,28–33], but virtually sepsis-free parenteral nutrition possible as shown by Sanderson and Dietel[34] who reported only one episode of infection in 100 patients treated for a total duration of 6·2 patient-years. The reported incidences also require careful interpretation. Incidence alone is not particularly meaningful as, for the same reported incidence of catheter-related sepsis from two centres, the results of the centre reporting

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the fewer episodes per patient-year of catheter use are obviously better

What constitutes catheter-related sepsis? A positive culture from blood drawn through a catheter may equally be due to bacteraemia arising from a pelvic abscess, for instance, as to organisms liberated from a colonized catheter. Furthermore, a scant growth of skin commensals from the tip of a catheter removed after uneventful use is much more likely to be due to contamination during withdrawal[35] than to catheter sepsis. Diagnosis of catheter-related sepsis requires that the same organism is grown from the catheter tip as is recovered from the blood[28] and that the clinical features of infection resolve on removal of the catheter. By these criteria, however, catheter-related sepsis can be proved only by removing the catheter, and some 'clean' catheters will inevitably be removed. Such wastage can now be avoided by using a recently described technique[36] which entails culturing samples of blood drawn simultaneously through the catheter and a peripheral vein. If the colony count in the catheter blood is five or more times that in the peripheral blood, catheter-related sepsis is highly likely. The high predictive value of this technique has been confirmed by others[37]. It should therefore no longer be necessary to remove catheters merely on suspicion of sepsis except in special circumstances

Catheters become infected either during insertion or subsequently through poor care. Catheters should be inserted with the same care as other prosthetic devices such as cardiac valves and artificial hips. A full aseptic technique is mandatory and reports of 'acceptable' infection rates in catheters inserted outside the operating theatre[11], in the author's opinion, set a dangerous precedent. The only acceptable infection rate following catheter insertion is zero. Not surprisingly the incidence of infection correlates directly with the number of attempts made at insertion[29] and inversely with the experience of the operator[33]. Prophylactic antibiotics do not appear to influence infection rates[38].

How then does an aseptically inserted catheter become infected? Because of the high standards now pertaining to their manufacture and storage, it is rare for feeding solutions to be the source of infection. The consensus of opinion is that infection arises from the catheter hub, which was found to be colonized by organisms in 70 per cent of patients with catheter-related sepsis in one study[39]. Regular dressing of the catheter exit site dramatically reduces the number of positive cultures from swabs taken from the exit site and the external portion of the catheter[40] and the value of strict catheter care protocols in reducing sepsis has now been confirmed by many centres worldwide. It has clearly been shown that catheter-related sepsis rates are lowest when catheter care is entrusted to designated nutrition nurses[41–43]

Until recently it was widely believed that placing the catheter in a subcutaneous tunnel reduced the risk of infection by preventing the migration of organisms from its hub to the intravenous portion. Controlled studies have shown that tunnelling does not in itself affect the infection rate[41,44,45] but it does enable the catheter to be brought out where it is easy to handle and dress, and this may indirectly reduce the potential for infection

The available data on infection rates in multipurpose catheters require careful appraisal. For instance Apelgren[46] found that 14·3 per cent of triple lumen catheters removed from patients in the intensive care unit were infected whereas Kaufman and colleagues[47] reported only a 3·8 per cent infection rate in multilumen catheters used in a similar setting. In both studies the catheters had been used for sampling, monitoring and administering drugs as well as for parenteral nutrition. The data reported by Pemberton and colleagues[48] offer an explanation for this discrepancy. They found a 19 per cent incidence of sepsis in triple lumen catheters compared with 3 per cent in single lumen catheters used exclusively for parenteral nutrition, yet the catheter exit site was infected in 5 and 3 per cent of cases respectively in the two groups. This suggests that although the catheter exit site was cared for equally well in patients with both kinds of catheter, infection was probably introduced into multilumen catheters during sampling, monitoring and the administration of drugs. It is well known that such procedures are not usually performed with the same regard to asepsis as that which pertains when parenteral nutrition solutions are set up. That infection may be introduced in this way has been shown in one study which found evidence of bacterial contamination of intravenous fluids in 50 per cent of the bags to which drugs had been added by the nursing staff on the ward[49]. Provided that a strict catheter care protocol is maintained, multilumen[43,50] or multiple[51] catheters are no more liable to become infected than single lumen catheters that are being used exclusively for parenteral nutrition

A logical way of protecting the patient from the dangers of contaminated solutions is to use bacterial filters. However, the filters which are most effective in trapping micro-organisms, i.e those with a pore size <0·2 μm, unfortunately also trap lipid particles. Although a larger pore size solves this problem, it does so at the expense of a reduced efficiency of microbial filtration and a clinical study using a 0·4 μm pore size for parenteral nutrition failed to show any significant reduction in infection rates[52]. This, combined with cost, has limited the application of filters in parenteral nutrition.

In a bench model, catheters can be consistently colonized by perfusion with solutions containing bacteria[53], but there are no clinical studies which have investigated the circumstances in which catheters can become infected by seeding from endogenous sources of sepsis. A higher catheter infection rate in the presence of a urinay tract infection has been reported[54] but in the author's experience catheter-related sepsis is uncommon in patients with intra-abdominal sepsis unless this is complicated by recurrent septicaemias. When catheters do become infected, the most common organisms are staphylococci (most often coagulase negative) and fungi[32].

Both antibiotic and antiseptic bonding of catheters are currently being evaluated. In an animal study, antibiotic bonding reduced the likelihood of bacterial colonization of the catheter over a considerable period[55]. Clinical trials of such devices are in progress but whatever the outcome their use should be restricted to special cases for fear of encouraging bacterial resistance and, worse still, colonization by fungi

In one study[56], catheter-related sepsis was reduced when heparin was added to the infusion solution, the explanation advanced being that heparin prevented the formation of a fibrin sleeve capable of supporting organisms. More recent work has failed to confirm the value of heparin[57], which is not surprising considering that electron microscopy of infected catheters has shown bacterial colonies attached to the surface without the aid of a fibrin sleeve[58].

How should catheter-related sepsis be managed? Catheter salvage rates of over 70 per cent have been reported simply by using a long course of appropriate antibiotics[59,60]. The author has not had any success with catheter salvage using antibiotics alone but has obtained encouraging results using a fibrinolytic agent (to clear the catheter of any surrounding infected clot) combined with an appropriate antibiotic. This approach, originally introduced to the Nutrition Unit at Hope Hospital by Professor Jeejeebhoy of Toronto, has been used to salvage four out of seven infected catheters. The following protocol was used. On suspicion of catheter infection, blood for culture is drawn through the catheter which is then 'locked' with a solution containing 5000 units urokinase and 1 g flucloxacillin. Intravenous feeding is discontinued and flucloxacillin started in maximal doses parenterally. If signs of infection do not resolve within 48 h the catheter is removed unless blood cultures reveal an organism resistant to flucloxacillin, in which case the procedure is repeated using an appropriate antibiotic. Parenteral nutrition is recommenced 48 h after clinical resolution of the infection.

Worthley recommends treating catheter-related sepsis by flushing the catheter with 2M hydrochloric acid[61]. Although I have no personal experience of this technique it makes sense to treat infection with an antiseptic rather than an antibiotic In this context, Taurolin® (Geistlich Sons Ltd., UK) is a promising intravenous antiseptic which I have used successfully for the treatment of catheter-related sepsis. Taurolin is a derivative of taurineamide and formaldehyde (bis(1,1 dioxoperhydro,1,2,4 methylene thiadiazinyl-4) methane), with a broad spectrum of activity against bacteria and fungi. It is non-toxic in man, being metabolized with a short half-life to taurine, carbon dioxide and water[62] There are few objective data on any of the methods described above for salvaging infected catheters and this area requires clarification by further research.

Infected catheters that cannot be salvaged will have to be removed. When vascular access is limited it is obviously an advantage if the catheter can be replaced over a guidewire. Infection of the new catheter has been shown to be no more likely if it is substituted for the infected catheter over a guidewire or placed at another site[28]. Replacement over a guidewire is economical with regard to access sites and intravenous feeding is not interrupted[29]. The technique is not, however, always feasible. Unless the replacement catheter is made of stiff material, vessel dilators and peel-apart sheaths will be required to create and maintain a track through which catheters made from very flexible material such as Silastic can be pushed. Furthermore it is now recognized that some degree of venous thrombosis is present in association with approximately 50 per cent of catheters (see below). Replacement over a guidewire may cause greater disturbance to the clot when compared with simple removal[63] and for these reasons it has been the policy at Hope Hospital to insert a new catheter at a different site

Venous thrombosis

Routine venography has shown that venous thrombosis complicates 45–59 per cent of catheters[2,64,65] and yet only 2·5–4·8 per cent of patients[4,12,66] have symptoms and clinical signs Possible aetiological factors include thrombogenicity of the catheter material, mechanical or 'osmotic' damage to the vein wall, and cumulative intimal damage from repeated catheterization of the same vein.

Thrombus can be seen surrounding the catheter within days of insertion[66,67]. Data from the United Kingdom Home Parenteral Nutrition Register did not reveal any correlation between the incidence of thrombosis and the duration of treatment[4], indicating that osmotic injury is not an important aetiological factor. There is also experimental evidence showing that the incidence of venous thrombosis is not related to the osmolality of the infusion solution[63].

The presence of catalysts and stabilizers used during the manufacture of catheters may encourage thrombosis[68] The material from which the catheter is made may also play a significant role. Bozzetti *et al* [63] found venographic evidence of thrombosis in 46·1 per cent of polyvinyl chloride catheters compared with 11·5 per cent of Silastic catheters. Polyurethane may be even less thrombogenic than silicone elastomer owing to the smoother surface topography of catheters made from it[69].

In one study, Hickman catheters were associated with a higher incidence of clinical major vein thrombosis compared with the smaller bore Broviac and uncuffed catheters[4]. However many patients with Hickman catheters had previously required replacement of their catheter on more than one occasion because of either recurrent occlusion or sepsis. In such cases the higher incidence of thrombosis was therefore likely to be a consequence of repeated catheterization

To minimize venous thrombosis it has been recommended that those patients requiring long-term parenteral nutrition should be anticoagulated[2,65] However, Ladefoged's group[2], which adopted and recommends such a policy, has reported death from subdural haematoma in one of their patients. To avoid such complications the value of partial anticoagulation has been studied. Heparin in a dose of 1 unit/ml of infusion fluid (amounting to 3000 units daily in the average case) did not decrease the incidence of venous thrombosis[63], but prospective controlled trials have shown a marked reduction in the incidence of venographically proven thrombosis in those given heparin at a concentration of 3 units/ml[70] and 20 000units every 24 h[71] On this evidence the amount of heparin given with the feeding solution at Hope Hospital was changed from 1 unit/ml to 3 units/ml from the beginning of 1987 because the incidence of clinical central venous thrombosis had been unacceptably high at about 4 per cent. It is too early to assess the effect of this measure.

Before employing anticoagulant regimens to minimize venous thrombosis it is well to keep the scale of the problem in perspective. First, we know that the incidence of thrombosis bears little relationship to the duration of catheter use and, second, over 95 per cent of patients do not manifest any clinical problems related to thrombosis even though routine venography shows evidence of thrombosis in up to 50 per cent of cases. For the present, a pragmatic approach would be to use heparin in a dose of 3 units/ml of nutrient solution until it is possible to identify more clearly those patients who are at greatest risk of developing thrombosis, and who might merit full anticoagulation. Jacobson and Brismar have found that patients with a haemoglobin concentration >12·7 g/dl before parenteral nutrition have a high risk of developing thrombosis[72]. If these findings are confirmed, they could provide a rational basis for selecting patients for full anticoagulation.

Management of clinically significant major vein thrombosis is a difficult problem. The usual presentation is with limb swelling or with the syndrome of superior vena caval obstruction. The recommended management of unilateral arm swelling is removal of the catheter, anticoagulation and elevation of the limb[73]. In the author's view it is not necessary to remove the catheter unless it is infected, the position of its tip is unsatisfactory, or its lumen is occluded The catheter can be left in place but is not used until the swelling has subsided while extension of thrombosis is prevented by anticoagulation for a period of 6 weeks.

The real challenge is posed by superior vena caval thrombosis, which carries a mortality rate of up to 50 per cent. In this condition the catheter is often removed when it ceases to function because its tip has become embedded in clot. However, if the lumen is patent the catheter should be left in place, removal does not relieve symptoms or hasten resolution of the thrombus and it removes vital central venous access. Additionally the catheter may be useful for the local administration of fibrinolytic therapy which has been used with dramatic success to clear the thrombus by some groups[74,75].

Central venous access can be gained in several ways when the original catheter is occluded and the superior vena cava, along with its major tributaries is thrombosed. The simplest method is to use the saphenous or femoral veins for access into the right atrium. Indeed in children, Mulvihill and Fonkalsrud[76] found that whereas the incidence of major vein thrombosis was 20 per cent in right atrial catheters inserted via the superior vena cava, the incidence of thrombosis of the femoral vein or the inferior vena cava from catheters inserted via the saphenous vein was only 4·9 per cent The same group has also shown that unlike superior vena caval thrombosis, it is rare to develop life-threatening or fatal complications as a result of inferior vena caval thrombosis[77].

Many ingenious ways of establishing vascular access have been described, and the choice depends on a careful clinical assessment, the results of venography and the available expertise. Venography may reveal large collateral veins leading into a patent portion of the superior vena cava and even the intercostal veins may become sufficiently large to enable a catheter to be passed into the right atrium via the azygos system[78]

If no satisfactory collateral veins can be found, it may be possible to introduce a guidewire from the femoral vein into the right atrium and, under X-ray control, to manipulate it through the clot in the superior vena cava into an accessible tributary such as the internal jugular vein. The guidewire is then recovered by exposing the vessel and a catheter is pulled forcibly into the right atrium using a Dormia basket passed over the guidewire This technique has been successfully used in three patients without morbidity or mortality[3]. Nevertheless it has the potential for serious complications, and is probably best reserved for patients in whom safer and simpler alternatives have failed, and only if special radiological expertise and facilities for dealing with the possible complications are available. In centres without the necessary special expertise, direct catheterization of the right atrium[79], although a major operation, is probably safer than the percutaneous method described above.

An option that is frequently not considered is to provide parenteral nutrition through an arteriovenous fistula. This has been used successfully by a number of centres[80,81] and, despite its drawbacks, may provide satisfactory access while allowing the central venous system to recover before further attempts are made at re-establishing central venous access.

The natural history of central venous thrombosis is unknown since there are no satisfactory longitudinal studies We know that partial thrombotic venous occlusions do resolve if treated early with anticoagulants, but it is not known whether the superior vena cava ever recanalizes after complete thrombotic occlusion. Refinements in isotope venography have put its diagnostic accuracy virtually on a par with contrast studies and its reliability in the diagnosis of catheter-related thrombosis has been established[82] This should permit repeated assessments of the venous system to study both the natural history of venous thrombosis and to identify a group of patients in whom full anticoagulation would be desirable.

Catheter occlusion

The incidence of catheter occlusion varies widely. A catheter may become occluded by blood clot, fatty deposits or calcium salts. Usually, fatty deposits consist of layers of lipid derived from the infused solutions A particularly high occlusion rate has been observed in association with the use of 'all in one' mixtures containing fat[83–85]. It has been postulated that the lipid particles coalesce and enlarge in certain circumstances when lipid emulsions are mixed with other solutions in a 'big bag' and tend, as a result, to precipitate onto the catheter. Catheter occlusion is much less frequent when lipid is administered separately from other nutrients[86] A case has been reported where biochemical analysis of the fatty material occluding a catheter showed it to consist of lipids derived from blood lipoproteins or cell membranes presumably due to reflux of blood into the catheter[87] However, only a single occluded catheter was studied and similar findings have not been reported by others.

Occlusion of a catheter can be prevented by ensuring that neither blood nor nutrient solution is allowed to stagnate within it for any length of time. If blood is drawn through the catheter, it must afterwards be flushed with a solution of heparin–saline. Nowadays parenteral nutrition commonly is given intermittently, usually during a 12-h period overnight, the catheter being 'locked' with heparin during the daytime This regimen, originally introduced to free the patient of the paraphernalia of parenteral nutrition during daytime, has almost certainly had the added bonus of reducing the incidence of catheter occlusion There is also some evidence that the addition of 1–3 units heparin to every millilitre of infusion solution (originally suggested as a prophylaxis for catheter infection[56]) may reduce the incidence of occlusion Non-refluxing catheters which do not need to be heparin locked are available and will prevent thrombotic occlusion but will still be prone to occlusion from deposition of lipid unless flushed[88]

Forceful flushing may easily rupture a blocked catheter and therefore the only safe solution for a totally blocked catheter is to replace it In most cases, however, occlusion is not sudden but is manifested by the need for ever-increasing pressure to maintain a satisfactory infusion rate An early sign of impending occlusion is the inability to aspirate blood through the catheter despite satisfactory infusion of fluids[89] In such cases, locking the catheter with a solution containing 5000 units urokinase is often successful[90]. The procedure can be repeated after 24 h if unsuccessful since the small dose of urokinase causes no serious coagulation abnormalities. Should fibrinolytic therapy fail, it may be worth flushing the catheter with 0·1 M HCl in case the occluding material consists of insoluble calcium salts[91].

The incidence of catheter occlusion can be minimized by adopting the preventive measures described above and indeed many patients have been on home parenteral nutrition for years without experiencing an episode of catheter occlusion.

Endocarditis and intracardiac thrombi

A literature search found only three published reports of catheter-related endocarditis[80,92,93]. Almost certainly there must be other reported cases but even if the actual number was ten times higher, it would still be surprisingly small considering that a catheter tip situated in the right atrium, and perhaps even abutting on the tricuspid valve, must present an ideal situation for seeding of the valve should the catheter become infected.

It is quite likely that catheter-related endocarditis is much more common than is appreciated and that repeated episodes of septicaemia in an individual are often ascribed to new episodes of catheter infection or to infection from some other known source of sepsis without the diagnosis of endocarditis ever being considered A post-mortem examination of a patient who died of recurrent septicaemia at Hope Hospital while on home parenteral nutrition showed unsuspected endocarditis with widespread metastatic abscesses.

Recently a number of cases of right atrial thrombus have been described. One patient who presented with features of a pulmonary embolus and sepsis was found to have a right atrial thrombus requiring surgery[9]. Another was noted to have a pansystolic murmur and calcification in the region of the right atrium on X-ray. Echocardiography confirmed a right atrial mass prolapsing into the right ventricle which was subsequently removed[10]. The condition has also been described in infants[6,7,94] and it may be fatal[8]. Like venous thrombosis, right atrial thrombi are probably often silent and may therefore be more prevalent than is appreciated Reed and colleagues have attempted to determine the natural history of this condition[95]. They noted superior vena caval or intracardiac thrombi at autopsy in 17 per cent of their leukaemic patients who died with functioning catheters and without any symptoms or signs of central venous thrombosis. The majority of thrombi were nodules measuring 1–2 cm in diameter attached firmly to the walls of the cava or the heart. Interestingly, although thrombi were most frequently found in patients who had had a catheter for at least 5 months, no thrombi were noted in cases where the catheter had been in place for more than a year

What is the fate of intracardiac thrombi? Mendoza and colleagues have reported two cases in infants where removal of the catheter and anticoagulation resulted in the complete resolution of large intracardiac thrombi over a period of 6 months[94]. The situation may not be as encouraging in the adult, for the 'resolution' of thrombi in the infant heart may be partly explained by the enlargement of the chambers with normal growth thereby making the attached thrombi appear to be decreasing in size

Research is urgently required in this direction because of the potentially fatal outcome of endocarditis and intracardiac thrombosis As yet there are few clues pointing to the aetiology. It has been suggested that the infusion of hyperosmolar dextrose solutions and the positioning of the catheter tip in the superior vena cava rather than in the right atrium may play an important part in the genesis of right atrial thrombosis[10] but detailed studies are awaited. Surveillance by echocardiography should now become routine in any patient on long-term parenteral nutrition[96] but care must be taken to avoid misinterpretation of echograms by artefacts projected by the catheter tip[92].

New developments

Currently most research is being directed towards developing less thrombogenic catheters and vascular access devices which are totally implantable.

It is now recognized that catalysts and stabilizers used in the manufacture of catheters are just as important in determining the thrombogenicity of a catheter as the material from which the catheter is made. Catheters made from new materials based on polytetramethylene ether glycol are being evaluated. They do not contain any stabilizers or catalysts and become extremely flexible at body temperature. Laboratory studies have shown that such catheters exhibit a lower affinity than Silastic catheters for platelets[97]. Another approach to reducing catheter thrombogenicity is to coat it with a hydrophilic polymer. The polymer swells by drawing water from the bloodstream and is claimed to have a low affinity for platelets both in laboratory tests and when implanted in animals (data from CardioSearch, Tampa, Florida, USA). The results of long-term clinical studies of its use are awaited.

The most commonly used totally implantable vascular access device in the UK is the Port-a-cath® (Pharmacia Ltd., Milton Keynes, UK). Although primarily intended to facilitate intravenous chemotherapy[98], Baptista and colleagues have successfully used it for parenteral nutrition for over a year in one patient[99]. The author's experience is less favourable. All four patients into whom the Port-a-cath was implanted for home parenteral nutrition found it unsatisfactory. Patients found that access to the portal by puncturing the overlying skin was both difficult and painful, demanding greater dexterity than was required for a conventional catheter. In two cases there was marked displacement of the catheter tip after satisfactory initial positioning with consequent axillary thrombosis in one. This propensity for tip displacement and a high incidence of central vein thrombosis associated with the use of the Port-a-cath has been reported by others[100,101]. I have therefore abandoned the use of this device for parenteral nutrition until devices more suitable for use with parenteral nutrition become available.

Conclusions

Many catheter-related complications are avoidable with careful attention to technique, both of insertion and subsequent use. Much needless morbidity and mortality can thus be avoided. It is now well established that the complication rate can be minimized if experience is concentrated in the hands of a few dedicated individuals forming a nutrition team.

In patients with difficult vascular access, careful planning and special expertise are essential and such cases should therefore be referred to specialist centres. More research is required into the pathophysiology of venous and right atrial thrombosis. In the meantime, patients on long-term parenteral nutrition should undergo regular isotope venography and echocardiography to identify problems at an early stage.

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Multiple authorship

The Editors remain concerned about the number of papers submitted to the Journal which appear to carry an inappropriate number of authors. We whole-heartedly endorse the recent statement by the International Committee of Medical Journal Editors, namely that authorship 'should be based only on substantial contributions to (a) conception and design, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and (c) final approval of the version to be published'. It must be stressed that these three criteria must *all* be fulfilled. Those submitting material to *The British Journal of Surgery* should be warned that the Editors intend to try to enforce these guidelines wherever possible.

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Femorofemoral bypass in unilateral iliac artery occlusion

Between January 1973 and January 1988, 188 patients with unilateral iliac artery occlusion were treated at The Middlesex and University College Hospitals, 185 for primary disease and three for blockage of a previous aortobifemoral graft. In the early part of the series, a variety of operations, including aortofemoral and iliofemoral bypass, and endarteriectomy, was used. Femorofemoral bypass was at first reserved for patients who were considered unfit for major surgery, but the results seemed so good that it was adopted as the procedure of choice. Latterly, percutaneous transluminal angioplasty became available, and the role of this is discussed. Over the 15-year period, 150 patients underwent femorofemoral bypass (all but two receiving a prosthetic graft). Of these, 90 per cent had disabling claudication and 8 per cent had critical ischaemia. There were six early deaths (within 30 days of operation) and five late deaths, and two surviving amputees; nine patients could not be traced. The remaining 128 patients have been assessed at intervals of from 3 to 92 months, both clinically and with Doppler studies. The cumulative patency was 86 per cent at 13 years, and all of these patients experienced subjective and haemodynamic improvement in the recipient limb. Eight grafts occluded in the early postoperative phase. In five patients there was deterioration in the donor limb; it is postulated that the effect was due to causes other than the operation. There were two serious postoperative complications due to technical error, one of which led to early above-knee amputation. These are presented in detail. In the light of this experience, the advantages and indications for femorofemoral bypass and the results to be expected from it have become clarified, and the technique standardized so that errors can be avoided. We suggest that femorofemoral bypass is now the operation of choice for unilateral iliac artery occlusion.

Keywords: Bypass, iliac artery

A. H. Fahal,
A. M. McDonald and
A. Marston

Bloomsbury Vascular Unit, The Middlesex and University College Hospitals, London, UK

Correspondence to:
Mr A. Marston, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK

The patient who presents with whole leg claudication due to unilateral iliac artery occlusion can be offered several treatment options including percutaneous transluminal balloon angioplasty, aortofemoral, iliofemoral or axillofemoral bypass, or varieties of endarteriectomy. The results of treatment for occlusions in these major vessels are on the whole good, in contrast to those obtained in the femoropopliteal segment. Most surgeons would treat a stenosis (as opposed to a complete occlusion) in this area by percutaneous transluminal angioplasty, which is simple and cost-effective, but at the same time would prefer open surgery in the case of complete occlusion. The simplest operation available is the femorofemoral bypass, originally described by Qudet and Beaconsfield in 1953[1]. In 1962 Vetto reported the first successful series of ten cases of unilateral iliac occlusion treated by this technique[2]. Initially the operation was reserved for poor-risk patients in whom intra-abdominal surgery was contraindicated[3], but the long-term results were surprisingly good and in 1983 our group reported an initial series of 66 patients[4]. We now present our definitive experience of the operation over 15 years.

Patients and methods

A total of 188 patients with unilateral iliac artery occlusion were treated at The Middlesex and University College Hospitals, London, between January 1973 and January 1988. Of these, 150 received a femorofemoral bypass, all but two receiving a prosthetic graft. There were 107 men and 43 women (71 and 29 per cent respectively). The age range was 42–82 years, with a median of 63. The symptoms requiring surgery were disabling claudication in 90 per cent, critical ischaemia according to the 1976 definition[5] in 8 per cent, and established gangrene in 2 per cent. Twenty patients (13 per cent) gave a previous history of myocardial infarct, angina or stroke. There were ten (7 per cent) diabetics in the series and nine (6 per cent) non-smokers. Of the 150 patients, 16 (11 per cent) had undergone previous aortoiliac surgery, including endarterectomy ($n = 8$), aortofemoral bypass ($n = 3$) or iliofemoral bypass ($n = 5$) which had been followed by reocclusion.

Patients were selected because of predominantly unilateral symptoms, confirmed by an absent or grossly weak femoral pulse on the affected side and a strong femoral pulse on the other side. Some of the patients in the early part of the study had stenoses rather than complete occlusions, and today would be managed by percutaneous transluminal angioplasty.

One advantage of this operative policy is that angiography is not always necessary. Retrograde (Seldinger) catheterization was carried out in 127 patients (85 per cent), but the combination of an absent femoral pulse and a viable limb is, for practical purposes, proof that the main upper channel of arterial supply, i.e. the profunda artery, remains open and is available for reconstruction.

Occlusion of the superficial femoral artery was not regarded as a contraindication to reconstruction either on the donor or the recipient side. In this series 20 patients (13 per cent) had an occluded superficial femoral artery on the symptomatic limb and five (3 per cent) had occlusion on the non-affected (donor) side. The arteries were blocked on both sides in three patients (2 per cent).

Pre- and postexercise Doppler ankle pressures were measured in all patients before surgery, immediately before discharge from hospital, and at each follow-up visit to the vascular clinic. The significance of differences were assessed by Student's t test and χ^2 analysis (with Yates' correction) as appropriate. Cumulative patency rates were determined by the modified life table method and results are expressed as mean ± s.d.

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Operative technique

At induction of anaesthesia 1·5 mg cefuroxime and 500 mg metronidazole were given, and repeated for two postoperative doses at 12 and 24 h postoperatively. The bladder was catheterized for 48 h.

With the patient positioned supine, the legs abducted, the catheter in place, and both groins prepared, short vertical incisions were made over the femoral bifurcations, taking care to avoid the lymphatics and saphenous nerves; the arteries were then mobilized and controlled An appropriately sized graft (in practice usually 8–10 mm) was then preclotted using the Sauvage technique, involving successive passages of blood and thorough irrigation with concentrated heparin

Our preferred technique is to place the graft behind the rectus abdominis muscle This gives a shorter and more direct route, and the prosthesis is protected from external pressure This route is contraindicated if the patient is very obese or has undergone previous pelvic surgery or radiotherapy (as was the case in six of our patients) There is no difficulty in developing this tunnel by blunt finger dissection, and the prepared tube can then be drawn from one incision to the other using a long aortic clamp (*Figure 1*)

After systemic heparinization, simultaneous anastomoses were carried out between the graft and the donor and recipient arteries It is attractive to have the tube lie in a 'lazy S' form, following the direction of blood flow but, in practice, it is often easier to place it horizontally (*Figure 2*), and this has no effect on subsequent performance[6] In our series there were 90 right-to-left grafts (60 per cent) and 60 left-to-right grafts. If the origin of the superficial femoral artery was occluded, the profunda branch was used as the recipient vessel, as was the case in six patients. In a further seven cases a profundoplasty was required Pressure was recorded in the donor and recipient vessels before and after graft placement, and abolition of the gradient was confirmed (*Table 1*)

Postoperatively, mobility was encouraged, two further doses of antibiotic were given at 12 and 24 h, and the urethral catheter was removed on the morning of the second day Most patients were able to leave hospital within 1 week of surgery.

Results

Of the 150 patients, six died within 30 days of operation (see below), five died after this period, and there were two surviving amputees (see below). Nine patients were lost to follow-up The remaining 128 patients have been assessed at intervals of from 3 months to a mean of 92 months.

Immediate morbidity and mortality

Eight elderly patients with rest pain and gangrene developed graft occlusion within 4 weeks of operation. All of these were high-risk patients with past histories of myocardial infarction and hyperlipidaemia whose preoperative Doppler pressures had been <40 mmHg. After amputation six of these patients died, the causes of death being pulmonary embolus, myocardial infarction and bronchopneumonia.

Four patients developed a chest infection, and local complications comprised two deep vein thromboses, four lymphatic fistulae (all of which healed spontaneously) and one wound infection. In one patient, who had received radiotherapy some years previously for carcinoma of the cervix, the graft eroded an adherent loop of small bowel, and the resulting faecal fistula and sepsis eventually led to removal of the graft and an above-knee amputation (we would now regard such a history as a total contraindication to femorofemoral bypass) One 77-year-old man had undergone a previous retropubic prostatectomy and his graft was (mistakenly) placed in the cave of Retzius. Apart from superficial inflammation of the wound his postoperative recovery was uneventful and he left hospital with good femoral pulses and relief of symptoms. He was referred to a urologist 3 months later because of frequency of micturition, and at the subsequent cytoscopy the graft, still pulsating, was seen to have eroded through into the bladder. The urine was sterile and the bladder was reconstructed behind the undisturbed graft, which continued to function thereafter.

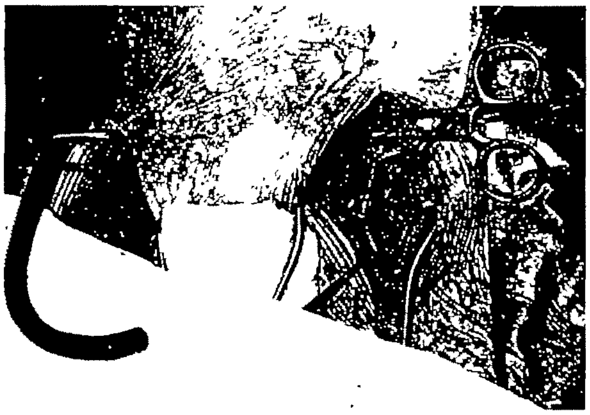

Figure 1 *Operative photograph showing passage of prosthesis*

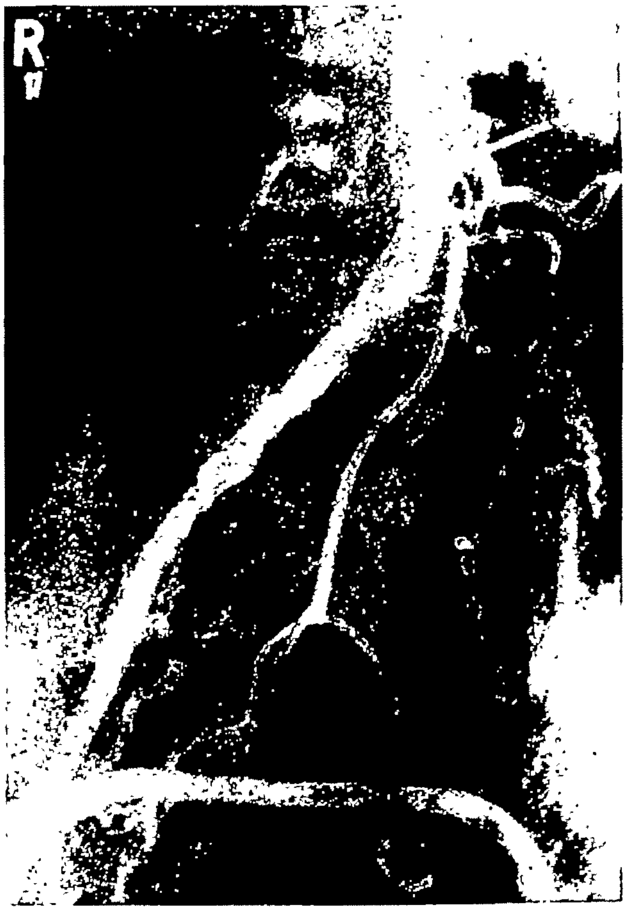

Figure 2 *Angiogram showing position of prosthesis (9 years after operation)*

Table 1 *Mean pressures in the radial artery and in donor and recipient common femoral arteries at the start and end of the operation*

	Radial (mmHg)	Donor (mmHg)	Recipient (mmHg)
Start of operation	120/85±20/10	130/80±15/9	79/65±10/8*
End of operation	110/70±12/12	125/75±9/5	120/75±10/11*

* $P<0.05$, recipient common femoral artery at the start *versus* the end of operation

Long-term follow-up

Follow-up took place at 1 and 3 months and at a final assessment, the average period of observation for the whole series being 92 months The results are shown in *Table 2* Symptoms were completely relieved at 1 month in 136 of the 140 patients with patent grafts (four closures), at 3 months in 118 of the 136 patients who had been asymptomatic at 1 month, and at

Table 2 *Doppler pressures and ankle brachial indices of patients with patent and occluded grafts (both early and late occlusion)*

	Patent graft (*n*=127)	Early (<4 weeks) failure (*n*=7)	Late (>4 weeks) failure (*n*=7)
Preoperatively			
Arm	150±26·3	154±20·5	160±17·5
Donor	120±25·4 (0·80±0·21)	140±22·8 (0·55±6·1)	120±20·5 (0·65)
Recipient	60±35·8 (0·42±0·15)	50±18 (0·25±0·11)	60±25·5 (0·29)
At 4 weeks			
Arm	152±26·4	142±41·9	155±16·4
Donor	130±25·4 (0·66±0·31)	105±21·3 (0·84±0·12)	100±37·9 (0·86±0·1)
Recipient	89±21·3 (0·79±0·18)	74±21·3 (0·35±0·25)	64±28·9 (0·4±0·18)
At final assessment			
Arm	142±13·9	140±31·6	148±31
Donor	120±19·9 (0·89±0·4)	120±25·7 (0·84±0·12)	130±24 (0·78±0·012)
Recipient	95±32 (0·85±0·15)	70±18 (0·30±0·034)	68±14 (0·28±0·013)

Ankle:brachial index in parentheses. Values are mean±s.d. (mmHg)

final assessment in 110 of the available 128 patients (86 per cent). Five patients out of the total series reported deterioration in the donor limb, all due to progression of their distal disease, and of these three required an amputation following closure of their femoropopliteal reconstruction. One patient underwent amputation of the recipient limb as a result of distal occlusion.

Patency rates. The cumulative patency at final assessment of the 128 available patients was 86 per cent No relation was noted to the sex of the patient, or to the side of the occlusion. All the patients who occluded their grafts had continued to smoke, and all had occlusion of the femoropopliteal segment on the recipient limb. The ankle systolic pressure on the affected side was <40 mmHg in all 15 cases. Three of them had undergone previous surgery for iliac occlusions.

Doppler pressure readings The preoperative Doppler pressures and ankle:brachial indices showed significant differences between the donor and recipient limbs, both at rest and after exercise ($P < 0{\cdot}05$). This gradient was abolished at the time of operation in all but the 15 patients who subsequently occluded their grafts. Of the others, there was significant improvement in the pressure in the recipient limb in 115 (90 per cent). Apart from the cases mentioned above, there was no deterioration in Doppler pressures on the donor side, either at early or late follow-up though, not unexpectedly, the preoperative ankle pressures on the donor side were lower in the patients with critical rather than severe ischaemia (*Table 2*).

Discussion

Although 25 years have passed since the original description of femorofemoral bypass[1], doubt is still sometimes expressed regarding the long-term patency and the effects on the donor limb[7]

The main attraction of the operation lies in its speed and simplicity, and the avoidance of intra-abdominal surgery in these often poor-risk patients. The operation is within the ability of any surgeon trained in basic vascular techniques and can if necessary be carried out under local anaesthesia[8] Although preoperative arteriography is useful in detecting proximal disease on the donor side, it can be dispensed with if the physical signs are clear-cut. A painful ischaemic leg with an absent femoral pulse, but with an easily felt pulse on the other side, usually predicts a satisfactory gradient We have previously reported[4] that an intraoperative gradient <25 mmHg indicates probable failure of femorofemoral bypass, and we would now carry out an iliofemoral or aortobifemoral bypass in such a case.

Our present policy is to perform Doppler pressure studies and a retrograde Seldinger aortogram and, if an iliac stenosis is found on the symptomatic side, to carry out a balloon angioplasty. In the presence of a complete occlusion, or if the angioplasty fails, the patient is entered on the next day's operating list for femorofemoral bypass.

Although femorofemoral bypass was originally reserved as a 'last ditch' operation for limb salvage in patients who were for some reason considered unfit for aortoiliac surgery, many surgeons, including ourselves, feel that the long-term results of this simple operation make it the procedure of first choice for patients with unilateral iliac occlusion who fulfil the usual criteria for surgical treatment. Given that the operation is safe and simple, its usefulness must be assessed by its complication rate (especially as regards the effect on the donor limb) and its long-term effectiveness. It is perhaps worthwhile to observe that 'long term' in this group of elderly and high-risk patients may involve periods of less than the conventional 5 years.

In general, the long-term results are satisfactory Harris *et al.*[9] reported a cumulative patency rate of 86 per cent at 4 years, which is identical to our own 14-year figure. Blaisdell *et al* [10] recorded a 2-year patency of 80 and 50 per cent, according to whether or not the distal arterial tree was occluded. Eugene *et al* reported a 30 per cent patency rate at 6 years[11] Apart from this last series, the figures suggest that femorofemoral bypass is at least equal in performance to major aortoiliac surgery[12].

The actual material used for the graft is probably not very important[13,14]. Our personal preference is for knitted material, for ease of preclotting. Morbidity and mortality rates are not easily compared because of unavoidable differences in case selection.

One considerable advantage of the femorofemoral bypass technique is the avoidance of the peri-iliac sympathetic plexus, disturbance of which may lead to erectile impotence[15,16] Indeed, the operation has been recorded as having a place in the restoration of penile blood supply[17]

Initial fears of a 'steal' phenomenon from the donor limb have not been realized. The study by Trimble *et al* [18], who reported two out of eight patients developing severe ischaemia in the donor limb, was not confirmed in an experimental study, nor in our own study (see above). The results of Harris *et al* [9], who reported a diminution in both exercise tolerance and ankle: brachial pressure indices, are also unconfirmed by our work, which agrees with the study of Dick showing that ankle:brachial ratios in the donor limb are unchanged after femorofemoral bypass[19]. There is also no evidence to support the suggestion that femorofemoral bypass potentiates disease in the donor side because of decreased flow

We conclude that femorofemoral bypass is simple, safe and effective in both the long and short term, and should be adopted as the procedure of first choice in patients with unilateral iliac artery occlusion who fulfil the accepted criteria for surgical relief.

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Risk of aortic aneurysm surgery as assessed by preoperative gated heart pool scan

J. P. Fletcher, V. F. Antico*, S. Gruenewald* and L. Z. Kershaw

*Departments of Surgery and *Nuclear Medicine, Westmead Hospital, Westmead, New South Wales, Australia 2145*

Correspondence to:
Mr J. P Fletcher

Gated heart pool scan measuring left ventricular ejection fraction (LVEF) was performed preoperatively in 72 patients presenting for elective repair of abdominal aortic aneurysm. Patients with a positive cardiac history were more likely to have a LVEF of $\leqslant 45$ *per cent* ($P<0\cdot001$)*. The operative mortality rate was 4 per cent. Each of three patients who died had a LVEF* $\leqslant 35$ *per cent and developed cardiac failure which led to renal failure. Five other patients developed cardiac failure manifested by acute pulmonary oedema during the early postoperative period. There was no statistically significant association between a positive cardiac history and the occurrence of postoperative cardiac failure or death. However, patients with a LVEF of* $\leqslant 45$ *per cent were more likely to develop postoperative cardiac failure* ($P=0\cdot004$) *while patients with a LVEF of* $\leqslant 35$ *per cent had a greater chance of dying* ($P<0\cdot001$)*. No patient died with a LVEF* >35 *per cent. Preoperative evaluation of LVEF can select patients at high risk of cardiac death from repair of abdominal aortic aneurysm. Such patients could be followed conservatively if they remain asymptomatic and the aneurysm does not enlarge. If operation is considered mandatory, patients with a low LVEF should receive intensive perioperative monitoring with enhancement of ventricular performance.*

Keywords: Aortic aneurysm repair, gated heart pool scan, left ventricular ejection fraction

The most frequent complication likely to lead to death following surgical repair of an abdominal aortic aneurysm is cardiac failure. Cardiac complications occur with greater frequency in patients known to have pre-existing coronary artery disease which may be evident from a history of previous myocardial infarction, angina or cardiac failure. However, some patients with significant coronary artery disease remain asymptomatic, and an additional investigation is required to identify patients at increased risk of death from cardiac complications following repair of abdominal aortic aneurysm.

From 1985, it has been our practice to obtain a gated heart pool scan preoperatively in patients presenting for elective repair of an abdominal aortic aneurysm. The purpose of this study was to assess the usefulness of this investigation in patients having aortic reconstruction for aneurysm disease.

Patients and methods

There were 72 consecutive patients studied over a 2-year period comprising 57 men and 15 women. Their ages ranged from 38 to 81 years with a mean age of 67·7 years (s.d. 7·4 years).

The presence of heart disease (history of myocardial infarction, angina, cardiac failure or abnormal ECG) was recorded for each patient and scored as 0 for no evidence of heart disease, 1 for previous history but currently asymptomatic, and 2 for symptomatic at the time of presentation.

Gated heart pool scan was performed preoperatively in the Department of Nuclear Medicine. Technetium-99 (^{99m}Tc) labelling of autologous red blood cells was performed by a modified *in vivo* method[1,2]. Stannous pyrophosphate was injected intravenously; 20 min later, 4 ml blood was withdrawn into a heparinized syringe containing 900 MBq ^{99m}Tc. This was then injected as a bolus after 10 min incubation. The patient was positioned supine under a small field of view γ camera which was rotated to the left anterior oblique position that best separated left and right ventricles. Data were entered onto a dedicated computer with 24 frames on a 64×64 matrix. At least 4×10^6 counts were acquired. Left ventricular ejection fraction (LVEF) was calculated by identifying the end-diastolic and end-systolic images. A region of interest was drawn around the left ventricle in each of the images, with a further region drawn to represent background[3,4]. LVEF equals end-diastolic counts minus end-systolic counts divided by end-diastolic counts. All counts were corrected for background. The normal range for LVEF in our department is 55–75 per cent.

All patients had a radial artery catheter inserted for perioperative monitoring of blood pressure which was kept as close to the preoperative level as possible by fluid and blood administration as required; nitroprusside was required in 10 patients at the time of aortic cross-clamping to control severe hypertension.

Postoperative course was recorded for each patient and scored as 0 for no cardiac complications, 1 for a cardiac complication from which the patient recovered, and 2 for death.

Data were entered into a microcomputer and analysed by Human Systems Dynamics (Northridge, California, USA) program using χ^2 analysis, Student's *t* test and multiple regression analysis.

Results

Of the 72 patients, 36 (50 per cent) had no history of cardiac disease, six (8 per cent) had a previous history but were currently asymptomatic and 30 (42 per cent) had symptoms of angina or cardiac failure at the time of presentation with their aneurysm (*Table 1*). LVEF ranged from 25 to 86 per cent with a mean of

Table 1 *History of heart disease related to left ventricular ejection fraction*

	n	LVEF$\leqslant$45%	LVEF>45%
No previous history	36	0	36
Previous history, now asymptomatic	6	3	3
Currently symptomatic	30	13	17

LVEF, left ventricular ejection fraction. Patients with a positive cardiac history were more likely to have a preoperative LVEF$\leqslant$45 per cent. χ^2 20·70, $P<0\cdot001$

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Table 2 *History of heart disease related to postoperative cardiac failure or death*

	n	Cardiac failure	Died
No previous history	36	3	0
Previous history, now asymptomatic	6	0	0
Currently symptomatic	30	2	3

Table 3 *Postoperative cardiac failure related to left ventricular ejection fraction*

	LVEF$\leqslant$45%	LVEF>45%
Cardiac failure	5	3
No cardiac failure	11	53

LVEF, left ventricular ejection fraction. Postoperative cardiac failure was more likely when preoperative LVEF $\leqslant$45 per cent: χ^2 8·45, P=0·004

56·1 per cent (s.d. 15·3 per cent). There was a strong association between cardiac history and LVEF (*Table 1*); patients with a positive cardiac history were more likely to have a LVEF of $\leqslant$45 per cent (P<0·001). A straight woven Dacron® (E. I. Dupont de Nemours Inc.) graft was used in 49 patients (68 per cent) and a bifurcated graft in 23 (bi-iliac graft in 21, bifemoral graft in two). There were three postoperative deaths—an operative mortality of 4 per cent. All three patients died from cardiac failure leading to renal failure. Five other patients developed cardiac failure manifested by acute pulmonary oedema during the early postoperative period (*Table 2*). There was no statistically significant association between cardiac history and the occurrence of postoperative cardiac failure or death.

There was no association between requirement for intraoperative nitroprusside administration for control of hypertension and the occurrence of postoperative cardiac complications.

Patients with a preoperative LVEF of $\leqslant$45 per cent (*Table 3*) were more likely to develop postoperative cardiac failure (P=0·004) while patients with a LVEF of $\leqslant$35 per cent (*Table 4*) had a greater chance of dying (P<0·001). No patient died with a LVEF >35 per cent.

Multiple regression analysis was performed using outcome as a determinant factor, and cardiac history and LVEF as predicting factors. Cardiac history was not a significant predictor (P=0·44) but LVEF was significant at predicting death and cardiac failure (P=0·01).

Discussion

Coronary artery disease is common in patients with abdominal aortic aneurysms and is the most frequent cause of operative mortality and later death in patients surviving surgery[5–8].

Advances in perioperative care have reduced the operative mortality of elective aneurysm repair, although late survival rates have remained constant[8,9]. Some investigators have performed haemodynamic studies to try to identify patients with abnormal cardiac function who would be at increased risk of developing postoperative cardiac complications. Pulmonary artery catheterization has been used preoperatively to measure cardiac output, cardiac index, right and left ventricular stroke work, and systemic and pulmonary vascular resistance. In one study in patients having elective vascular surgery, only 33 per cent of patients had normal left ventricular function[10]. Maintenance of optimal cardiac index during the perioperative period has been shown to reduce the incidence of postoperative cardiac complications in patients having repair of abdominal aortic aneurysm[11].

Table 4 *Postoperative death related to left ventricular ejection fraction*

	LVEF$\leqslant$35%	LVEF>35%
Died	3	0
Survived	7	62

LVEF, left ventricular ejection fraction. Patients with a preoperative LVEF$\leqslant$35 per cent were more likely to die: χ^2 19·41, P<0·001

Routine preoperative pulmonary artery catheterization is impractical at our institution because of pressure on intensive care beds. Furthermore, it is not possible for all patients to be managed routinely in intensive care postoperatively. It is therefore important to identify patients especially at risk of postoperative cardiac complications so that intensive care facilities can be made available for this group while patients at less risk bypass the intensive care ward.

The presence of coronary artery disease can be assessed by careful history and management decisions made accordingly[12,13], but in our study history alone was not significant in predicting the risk of cardiac complications developing postoperatively.

Stress electrocardiography is often used as a non-invasive screening test to select patients for coronary angiography. However, false positive rates of 16–40 per cent and false negative rates of 15–33 per cent have been encountered with some 24 per cent of patients being unable to complete the exercise testing because of claudication or dyspnoea[14,15]. The incidence of false negative stress electrocardiography may be greater when there is a high prevalence of coronary artery disease in the population being tested[16], such as would be the case in patients presenting with aortic aneurysm.

Routine screening of all patients presenting for vascular reconstructive procedures with coronary angiography has been performed [17], but is invasive and is not practical for most institutions.

Non-invasive radionuclide assessment of cardiac function by measurement of LVEF[18] is useful for identifying patients at increased risk of developing postoperative cardiac complications. Methods other than gated heart pool scan are available and involve use of M-mode and two-dimensional echocardiography with or without Doppler[19–22]. However, not all patients can be imaged successfully owing to limited access to the heart because of over-expanded lung fields, a problem frequently encountered in patients with cardiovascular disease who have an increased incidence of chronic obstructive airways disease. Successful examination is possible in only some 84 per cent of patients[21]. In our series, no patient was excluded because of inadequate gated heart pool scan.

Ideally, LVEF should be combined with an assessment of coronary artery status; we are currently investigating the usefulness of dipyridamole thallium scanning for detecting the presence of significant coronary artery disease in patients undergoing arterial reconstruction.

Our findings of increased risk of cardiac complications occurring in patients with a low ejection fraction are in agreement with those of Fiser *et al.*[23] and Mosley *et al* [24]. We support their conclusions that preoperative evaluation of ejection fraction can select patients at high risk of cardiac death following abdominal aortic operation. Such patients can be followed conservatively if asymptomatic[25], or, if surgery is considered essential, intensive perioperative monitoring with enhancement of ventricular performance is recommended.

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Plasma arginine vasopressin levels and arterial pressure during open heart surgery

W. G. A. Woods,
M. L. Forsling* and
L. P. Le Quesne

*Departments of Surgical Studies and *Physiology, The Middlesex Hospital Medical School, London, UK*

Correspondence to
Mr W G A Woods,
The London Hospital,
London E1 1BB, UK

A study of plasma arginine vasopressin (AVP) levels and their relation to changes in arterial pressure was undertaken in 13 patients undergoing open heart surgery. Seven of the patients received high doses of intravenous morphine (1 or 2 mg/kg) as part of their anaesthetic, whereas the other six did not. Increases in the AVP levels during cardiopulmonary bypass (CPB) were significant in both groups, but were significantly greater in the patients not receiving morphine (median 86·1 fmol/ml) than in those who did (47·5 fmol/ml). In both groups there was a linear correlation between the natural logarithm of the plasma AVP level and the percentage fall in the mean arterial pressure, although the slope of the relationship was significantly less in the group receiving morphine than in the group not receiving morphine. These results indicate that in patients undergoing cardiac surgery the neuroendocrine reflex control of plasma AVP levels in relation to changes in arterial pressure is intact, but that the sensitivity of the reflex (i.e. the increase in plasma AVP level for a given fall in arterial pressure) is reduced by the administration of high doses of intravenous morphine.

Keywords: Vasopressin, operative surgery, arterial pressure

In 1953 Le Quesne and Lewis[1] observed that after surgical operations not only was there a reduction in sodium excretion, but there was also a separate and specific defect of water excretion. They inferred that this was due to the secretion of increased amounts of arginine vasopressin (AVP). Subsequent measurements of plasma AVP levels both by bioassay[2] and by radioimmunoassay[3] have confirmed this. Studies in the anaesthetized human undergoing surgical operations have variously attributed different proportions of the increases in levels of the hormone to the fluid depletion of the overnight fast[4,5], preoperative anxiety[6], the induction and maintenance of anaesthesia[3], and changes in extracellular fluid volume[7]. The very high levels recorded during laparotomy[2], and sternotomy and cardiopulmonary bypass (CPB)[5] have usually been attributed to unquantifiable variables such as visceral manipulation[2], pain[4], or the magnitude of the operative trauma[3]. Philbin and Coggins[8] concluded that 'stress' was a stimulus to AVP release, from their observation that high doses of intravenous morphine prevented any rise in plasma AVP levels during open heart surgery in the period before CPB.

Studies in experimental animals and conscious humans[9] have clearly shown that not only is falling arterial pressure a potent stimulus to AVP release but also that the relationship between the two variables can be expressed mathematically. Cochrane *et al.*[10] suggested that falling arterial pressure might be an important stimulus in the anaesthetized subject, but there has been no formal study of the relationship between these two variables during surgical operations. This study was therefore designed to test the hypothesis that falling arterial pressure is an effective stimulus to AVP release in patients undergoing surgical operations. Patients undergoing open heart surgery were chosen because of the large changes in arterial pressure often associated with these operations and the small changes in plasma osmolality, which thus tended to isolate the arterial pressure as a possible stimulus, and because of the comparative ease of obtaining a continuous record of the arterial pressure and frequent blood samples. Seven of the patients were given high doses of intravenous morphine in the light of its inhibitory effect on AVP levels, as demonstrated by Philbin and Coggins in similar patients[8].

Patients and methods

Studies were performed on 13 patients who underwent a variety of cardiac operations, all requiring the use of CPB. Patients in atrial fibrillation were excluded, as were children, in whom the sampling volumes would have been unacceptably high, and patients deemed by the anaesthetist to be unsuitable candidates for the high dose intravenous morphine regimen. Suitable patients (i.e. those in whom either anaesthetic technique was equally acceptable) were then randomly allocated to one of two groups: those receiving morphine (MORPH) or those not receiving morphine (NOMORPH). There were six patients in the NOMORPH group, all of them men, with an average age of 49·2 years (range 34–61). Three of them underwent coronary artery bypass grafting and three aortic valve replacement. There were seven patients in the MORPH group, six men and one woman with an average age of 58·6 years (range 49–66). Four of these patients underwent coronary artery bypass grafting, two underwent aortic valve replacement and one had a resection of a left ventricular aneurysm. All the patients having coronary artery bypass grafting were receiving treatment for angina consisting of varying combinations of a β-blocker, nifedipine, and glyceryl trinitrate.

Premedication consisted of Omnopon (Roche Products Ltd., UK) or diamorphine and hyoscine, and anaesthesia was induced with thiopentone and pancuronium. Anaesthesia was maintained in the NOMORPH group with halothane, nitrous oxide, and oxygen. In the MORPH group, patients received either 1 or 2 mg/kg body weight morphine sulphate, given intravenously over approximately 3 min, shortly after the induction of anaesthesia which was supplemented with nitrous oxide and oxygen. During CPB, Althesin (Glaxo Laboratories, Middlesex, UK) and droperidol were also used in some patients.

Arterial pressure was measured continuously from a cannula placed in the radial artery immediately after induction of anaesthesia. This was connected to a pressure transducer (AE 840, A.M.E., Horten, Norway) and dome (AE 841, A.M.E., Horten), whose electrical output was fed to an SE 905 transducer/converter (S.E. Laboratories, Feltham, UK). The output from the latter was continuously displayed on a chart recorder (Gould Brush 220, Gould Medical UK, Lutterworth, UK). Arterial pressure recording before the insertion of the radial artery cannula and its connection to the recording equipment were carried out using Dinamap Adult Paediatric Vital Signs Monitor Model 845 (Kritikon, Tampa, USA), which was shown to correlate well with the direct radial artery measurement (correlation coefficient $r = 0{\cdot}98$, $n = 44$, $P < 0{\cdot}001$)). The blood pressure corresponding with each blood sample was recorded as the minimum mean pressure in the 10-min interval after the preceding sample (see below).

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Table 1 *Median plasma arginine vasopressin concentration, median percentage fall in mean arterial pressure and median percentage fall in plasma osmolality for patients in the two groups for each of six periods in the operation*

Period recording		[AVP] (fmol/ml)		Δ MP		Δ OSM	
No.	Description	NOMORPH	MORPH	NOMORPH	MORPH	NOMORPH	MORPH
1	Before premedication	2·3	3·3	—	—	0	0
2	Before induction	2·1	2·2	—	—	0·15	0
3	Before skin incision	2·4	5·8	19·8	16·5	−0·3	−0·3
4	During vein harvest‡	2·3	1·8	29·8	21·9	−0·35	0
5	After thoracotomy	25·3*†	13·7	36·7	25·2	−0·3	0
6	Cardiopulmonary bypass	86·1*†	47·5†	63·8*†	46·6†	1·1	1·1

* Indicates a significant difference when compared with levels during the same period in the other group, † indicates a significant change over initial levels, ‡ only contains data from those patients having coronary artery bypass grafting, [AVP], arginine vasopressin concentrations, Δ MP, percentage fall in mean arterial pressure, Δ OSM, percentage fall in plasma osmolality

Table 2 *The y intercept, regression coefficient and correlation coefficient for individual NOMORPH patients*

Patient	y intercept (*a*)	Regression coefficient (*b*)	Correlation coefficient (*r*)
A	2·11	0·04	0·77
B	−0·91	0·088	0·84
C	2·38	0·042	0·93
D	−0·24	0·087	0·67
E	−0·47	0·057	0·89
F	0·56	0·067	0·57
Mean*	0·57	0·063	

* Mean of a and b, for the equation $\ln[AVP] = b\Delta MP + a$ where ΔMP is the percentage change in mean arterial pressure

In order to allow direct comparison with the results of Robertson[9], the percentage fall in the mean arterial pressure (ΔMP) was calculated, and subsequently this value was used in all calculations. ΔMP was calculated in each patient as the percentage reduction from the maximum mean arterial pressure recorded for that patient following induction of anaesthesia

Blood samples of 6 ml were taken immediately before premedication, immediately before induction of anaesthesia, and thereafter every 10 min until the end of CPB The first two samples were taken from a peripheral vein, usually in the antecubital fossa Subsequent samples were taken from a catheter in the superior vena cava, placed via the internal jugular vein by direct skin puncture. Samples were immediately centrifuged and the supernatant removed One aliquot of this was put in dry ice and subsequently stored at −20°C to await AVP assay The other aliquot was used for the immediate determination of the plasma osmolality and the plasma protein concentration.

Plasma AVP levels were measured by radioimmunoassay, by a modification of the method of Forsling and Williams[11] The intra-assay coefficient of variation was 7·7 per cent and the interassay coefficient of variation 11·9 per cent. AVP levels during CPB were corrected to allow for the change in the volume of distribution of the hormone caused by the extracorporeal circulation. Under normal circumstances the hormone is thought to equilibrate with the extracellular fluid[12]. Since the pump-priming fluid was protein free, the AVP concentration during CPB was multiplied by the ratio of the plasma protein concentration immediately before instituting CPB and the plasma protein concentration immediately after instituting CPB Plasma osmolality was measured using the Knauer Halbmicro (Knauer, Heidelberg, FRG) freezing point depression osmometer Plasma protein concentration was measured using a table model clinical refractometer (Avap Optical Works Company Ltd , Tokyo, Japan

For comparison of AVP levels at different stages in the operation the samples were grouped together in six periods period 1, the time before premedication, period 2, after premedication and before induction of anaesthesia; period 3, after induction and before the initial skin incision, period 4 (only in those patients who had coronary artery bypass grafts), during the dissection of the long saphenous vein and before median sternotomy, period 5, from median sternotomy until the establishment of CPB, period 6, the time on CPB

Data were stored on a CDC Cyber 174 computer (Control Data, Minneapolis, USA), and statistical computation was carried out using the statistical software package MINITAB[13] AVP levels for different periods in the operation were compared using the Mann–Whitney *U* test Linear regression analysis was used to regress the natural logarithm of the plasma AVP concentration (ln[AVP]) against the ΔMP

All the patients gave their informed consent to the study, which was approved by the ethical committee of The Middlesex Hospital

Results

Changes in plasma AVP concentration

Table 1 shows the median plasma AVP concentrations in the two groups. There were no statistically significant changes over the levels in period 1 (NOMORPH 2·3 fmol/ml; MORPH 3·3 fmol/ml) in either group in periods 2, 3 or 4. The level in period 5 (after thoracotomy) reached 25·3 fmol/ml in the NOMORPH group which was significantly higher than the levels reached in the previous periods and higher than the level for the same period in the MORPH group (13·7 fmol/ml), the latter, however, was not higher than preceding levels in this same group. In period 6 (on CPB) the level in each group was significantly higher than in the premedication period, and the level in the NOMORPH group (86·1 fmol/ml) was significantly higher than that in the MORPH group (47·5 fmol/ml).

Percentage changes in mean arterial pressure

There were statistically significant falls in arterial pressure in period 6 (on CPB) in each group, and the fall was significantly greater in the NOMORPH group that in the MORPH group (*Table 1*).

Correlation of ln[AVP] with ΔMP

In the NOMORPH group there was a linear correlation between the plasma ln[AVP] and ΔMP *Table 2* shows the *y* intercept, the slope or regression coefficient and the correlation coefficient for each patient. The linear correlation is borne out by an inspection of scatter diagrams for individual patients (*Figure 1*). The same statistics for the MORPH group appear in *Table 3*. *P* values have not been calculated for these correlations in view of the tendency for serial correlation in the data from each patient owing to the sequential nature of the observations. However, it can be demonstrated that the regression coefficients for both the MORPH and the NOMORPH groups are positive and differ significantly from zero ($P < 0·05$, Wilcoxon signed rank test).

Comparing the regression coefficients in the two groups it can be shown that the slope for the NOMORPH patients is significantly steeper than that for the MORPH patients ($P < 0·01$, Wilcoxon signed rank test).

Changes in plasma osmolality

The changes in plasma osmolality (*Table 1*) were small and only reached significance between periods 5 and 6 in the NOMORPH group.

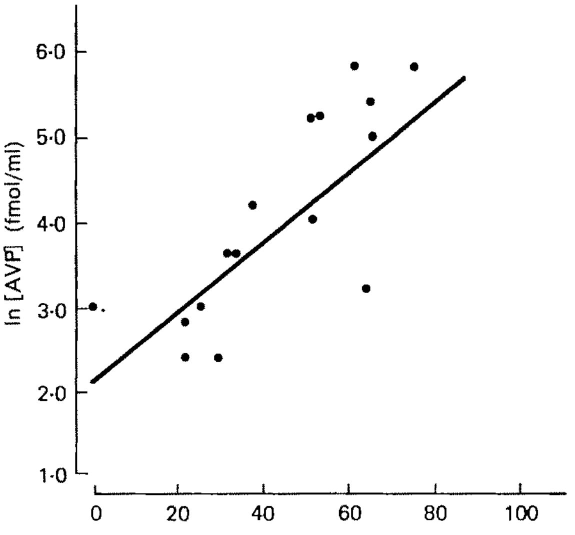

Figure 1 *The natural logarithm of the median plasma arginine vasopressin concentration (ln[AVP]) plotted against the percentage fall in mean arterial pressure for one of the patients in the group receiving no morphine Correlation coefficient r = 0·77*

Table 3 *The y intercept, regression coefficient and correlation coefficient for individual MORPH patients*

Patient	y intercept (a)	Regression coefficient (b)	Correlation coefficient (r)
G	0·599	0·04	0·47
H	3·613	0·012	0·49
I	−0·246	0·048	0·43
J	1·627	0·015	0·16
K	2·29	0·041	0·94
L	0·622	0·033	0·11
M	2·428	0·035	0·18
Mean*	1·56	0·032	

*Mean of a and b, for the equation ln[AVP] = bΔMP + a where ΔMP is the percentage change in mean arterial pressure

Discussion

The pattern of change in plasma AVP levels during the course of the operations in this study was consistent with previously published findings. Basal levels were within the normal 'unstimulated' range quoted by most authors (e.g Forsling and Williams[11]), and the lack of any significant change in plasma AVP levels in either group in periods 2 (before induction) and 3 (after induction) is consistent with the view that neither premedication[8] nor induction of anaesthesia[2,8] has any significant effect on plasma levels of the hormone. Similarly, the lack of any significant change in AVP levels during period 4, while the saphenous vein was being harvested, accords with the observations of Nashat[14] in the greyhound, although Moran *et al*[4] did record small rises in AVP levels during skin incision unless regional anaesthesia was used. The values obtained for period 5 (after median sternotomy) are in agreement with those of Philbin and Coggins[8] in that the levels in the group which received no morphine were significantly elevated (median 25·3 fmol/ml) whereas in the MORPH patients the levels, although elevated, were not significantly so. The explanation offered by Philbin and Coggins was that morphine was suppressing the stress response Simpson and Forsling[15], reporting similar findings, suggested the alternative explanation that the use of halothane might itself be associated with increased AVP levels. Others have found either no specific stimulation of AVP release by halothane[7,16] or have suggested that any increase in AVP levels associated with halothane was secondary to the cardiovascular effects of the drug[17] The evidence presented here tends to support the latter view in that not only was there a correlation with arterial pressure in both groups (i e those receiving halothane and those not receiving halothane), but also falls in arterial pressure were greater in the patients receiving halothane. Any specific stimulation of AVP secretion by halothane would therefore have to be separate from the effect of falling arterial pressure. The difference in the sensitivity or slope of the relationship (see below) between ln[AVP] and the fall in arterial pressure in the MORPH and NOMORPH groups of patients might have been an effect of the halothane in the NOMORPH group or the morphine in the MORPH group.

The findings in this study clearly show a correlation between the ln[AVP] and the ΔMP. This has not previously been reported in anaesthetized subjects undergoing surgical operations. It has previously been shown by Robertson[9] that in conscious human subjects rendered hypotensive with the ganglion-blocking agent trimetaphan there is a correlation between these two variables that is described by the equation:

$$\ln[AVP] = 0{\cdot}11\Delta MP + 0{\cdot}34$$

The equation for the NOMORPH patients in the present study, derived by taking the mean of the values for the intercept and regression coefficients from each patient, is.

$$\ln[AVP] = 0{\cdot}063\Delta MP + 0{\cdot}57$$

and that derived for the MORPH patients is:

$$\ln[AVP] = 0{\cdot}032\Delta MP + 1{\cdot}56$$

When plotted these equations describe the straight lines shown in *Figure 2.*

The demonstration of a correlation does not of itself imply a causal relationship between two variables. However, it is widely accepted that the relationship observed by Robertson[9], and described by the equation set out above, does imply a causal link between a fall in arterial pressure and a rise in the plasma AVP concentration, this relationship being dependent upon the functional integrity of the carotid sinus[18] and its nerve supply[19] The findings in the NOMORPH group that the relationship of the fall in arterial pressure to the AVP level and the slope of this relationship are similar to those found by Robertson in normal adults[9] strongly suggest that this causal

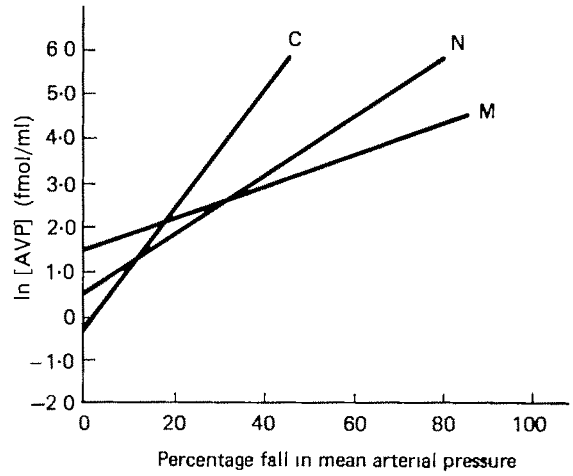

Figure 2 *Regression lines for the relationship ln[AVP] = bΔMP + a in the patients in the group receiving no morphine (N), and in the patients in the group receiving morphine (M), calculated from the mean values for* a *and* b *(Tables 2 and 3), and in conscious subjects (C Robertson[9]) ln[AVP], the natural logarithm of the median plasma arginine vasopressin concentration,* a, *y intercept,* b, *regression coefficient, ΔMP, the percentage fall in mean arterial pressure*

relationship is maintained during these operations The smaller value for the regression coefficient (a measure of the slope of the regression line) in this group of patients compared with the value obtained by Robertson may be interpreted as a reduction in the gain or sensitivity of the neuroendocrine reflex caused probably by one of the anaesthetic agents The still greater (and statistically significant) reduction in the regression coefficient in the MORPH patients may similarly be interpreted as a depressant effect of the morphine on the sensitivity of the reflex. This is consistent with, and may provide an explanation for, the observation of Philbin and Coggins[8] that high doses of intravenous morphine apparently inhibit the secretion of AVP There is much support for the view that opiates have a depressant effect on AVP levels, both when given systemically and by the intracerebroventricular route[20], although the traditional view[21] was that morphine stimulated the release of AVP. Reconciliation of this apparent paradox may have come from the observations of Aziz *et al.*[22] who have shown that the effect of intracerebroventricular morphine may be either inhibitory or stimulatory depending on the dose, the timing, and probably the state of hydration as well. Despite the balance of evidence from other sources it is not possible from the data presented here to refute the alternative hypothesis that the effect on the sensitivity of the reflex demonstrated here is due to an increase in gain or sensitivity caused by halothane in the NOMORPH group rather than to a reduction in sensitivity caused by the morphine in the MORPH group.

It is suggested that the relationship between plasma AVP level and falling arterial pressure is well seen in these patients because the large changes in arterial pressure swamp other possible stimuli to AVP secretion, in particular changes in osmolality, which were small, and the secretion which may be associated with pain[4], opening coelomic cavities[23], visceral traction, and other various operative stimuli

These results provide strong evidence that, in patients undergoing open heart surgery, the neuroendocrine reflex control of plasma AVP levels in relation to changes in arterial pressure is intact, but that the gain or sensitivity of the reflex is reduced by the administration of large doses of intravenous morphine. The pathophysiological logic of the graded secretion of one of the most powerful vasopressor substances known in response to a fall in arterial pressure is compelling It was perhaps naive to refer to this aspect of the endocrine response to surgical operations as the 'inappropriate' secretion of AVP

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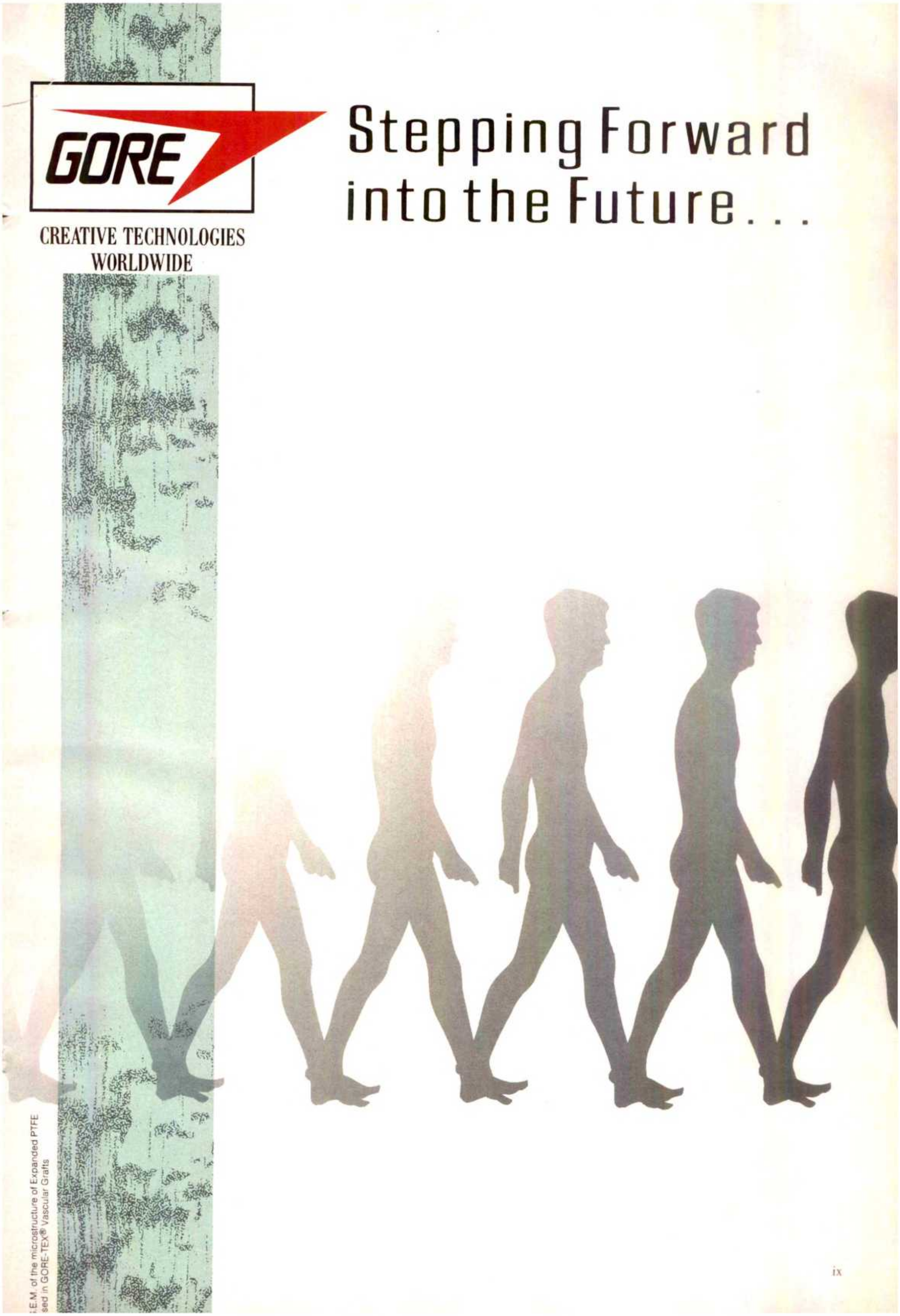

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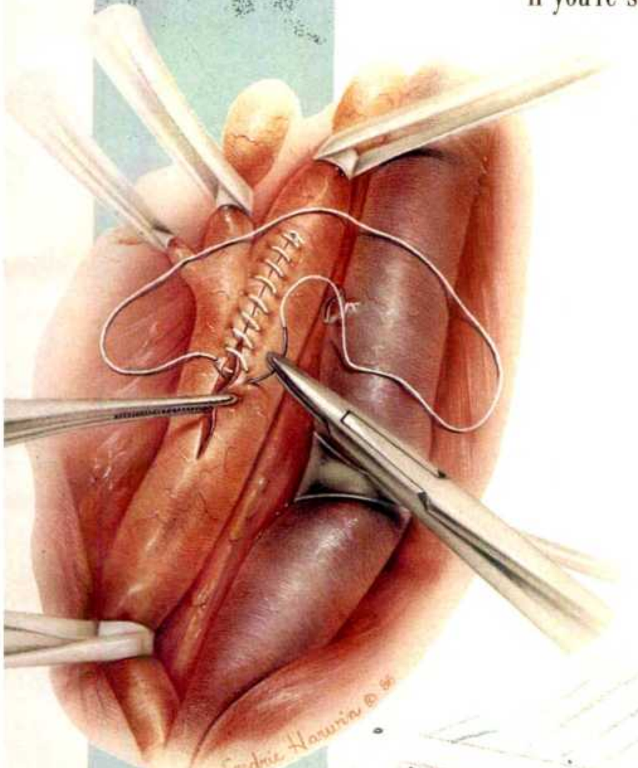

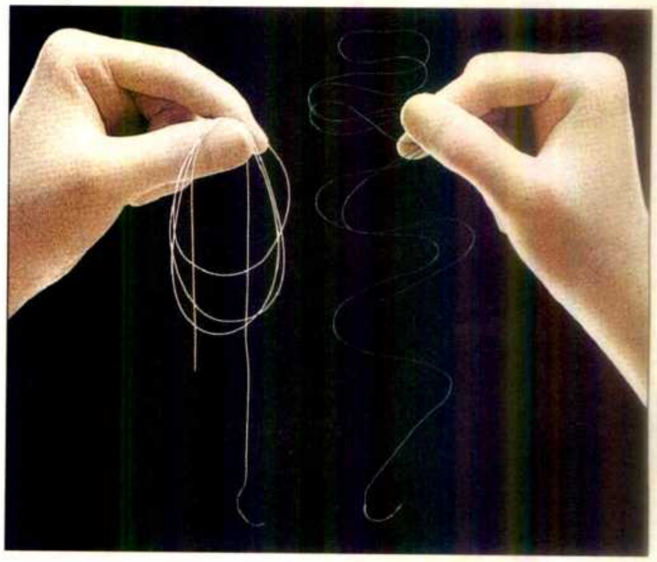

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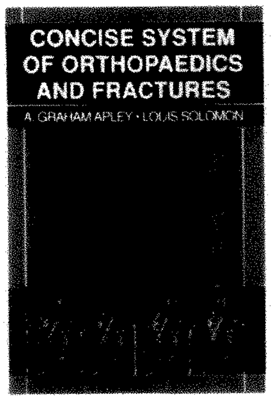

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Carotid body tumours and other cervical paragangliomas: diagnosis and management in 25 patients

G. A. D. McPherson, A. W. Halliday and A. O. Mansfield

Department of Vascular Surgery, St. Mary's Hospital, Praed Street, London W2 1NY, UK

Correspondence to:
Miss A. O. Mansfield

This report of a series of 25 patients with cervical paragangliomas reviews the experience of one surgeon over a period of 13 years. A total of 26 resections were performed with no mortality and no hemiplegia. Two patients required carotid reconstruction. Eight patients had a permanent cranial nerve palsy but in seven this was due to involvement of the nerve by the tumour. Lymph node involvement occurred in two patients. Only one patient has developed recurrent tumour. These tumours are locally malignant and resection offers a chance of cure.

Keywords: Cervical paraganglioma, diagnosis, management

The carotid body is a small chemoreceptor organ measuring 7 × 4 mm and lies buried in the adventitia in the posterior aspect of the common carotid bifurcation. First described by Haller[1] in 1743 it is now known to be involved in the reflex control of heart rate, blood pressure and respiration via the chemical composition of blood and its temperature and forms part of an extensive chemoreceptor system. Tumours of this tissue were originally described as chemodectomas by Mulligan (1950)[2] and the most common of these are carotid body tumours. These form part of a widely distributed group of tumours known as paragangliomas.

Carotid body tumours are rare (an incidence of 0·012 per cent of surgical specimens at one hospital has been reported)[3]. The diagnosis can present considerable hazards and inexperienced removal can be disastrous. Matthews observed in 1915[4] that 'this rare tumour presents unusual difficulties to the surgeon and should he encounter it without having suspected the diagnosis, the experience will not soon be forgotten.' This paper describes a series of 25 patients presenting over 13 years and examines trends in diagnosis and management.

The first successful excision of a carotid body tumour was reported by Maydl in 1886[5]. Unfortunately the patient was hemiplegic and aphasic after the operation. In 1889 Albert managed to excise a carotid body tumour without ligation of the carotid vessels[6]. However, a persistently high mortality rate for resection of carotid body tumours, around 30 per cent, led Martin *et al.*[7] to state in 1957 that these tumours should be subject to biopsy only. As recently as 1971, Shamblin *et al.*[8] from the Mayo Clinic reported 16 cerebrovascular accidents in 72 operative procedures, probably the largest published series, and as a result of this study they proposed a surgical classification of carotid body tumours as follows: group I, easy to remove from adjacent vessels; group II, intimate attachment to the carotid artery requiring dissection in the subadventitial plane[9]; group III, where there is transmural invasion of the carotid artery by the tumour. Approximately half of the tumours in their series fell into group II, the other half being distributed between groups I and III. More recently a pathological classification has been proposed by Glenner and Grimley[10]. Carotid body tumours and chemodectomas arising from the glomus jugularis and chemoreceptor tissue around the lung are grouped together in this classification and called the branchiomeric paragangliomas as opposed to the intravagal or aorticosympathetic paragangliomas. The distribution of branchiomeric paragangliomas is shown in *Figure 1*. Glenner and Grimley[10] have suggested that paragangliomas should be classified according to anatomical site and functional activity. Thus the precise nomenclature for a carotid body tumour is 'carotid body paraganglioma non-functional'. Paragangliomas may occur synchronously in about 10 per cent of patients and while carotid body tumours are not functionally active, other branchiomeric and aorticosympathetic paragangliomas may be functionally indistinguishable from phaeochromocytomas. Finally, where there is a family history the tendency to multicentricity is much higher[11].

Patients and methods

Between 1975 and 1987, 25 patients, median age 47 years (range 17-61 years), were referred to one surgeon (A.O.M.) (*Table 1*). Sixteen were women and nine were men. Twenty patients had single carotid body tumours and two patients had bilateral carotid body tumours. In two patients the tumour was associated with functioning middle mediastinal paragangliomas and one further patient had a carotid body tumour with bilateral adrenal phaeochromocytomas and a para-aortic phaeochromocytoma. Three others had vagal paragangliomas.

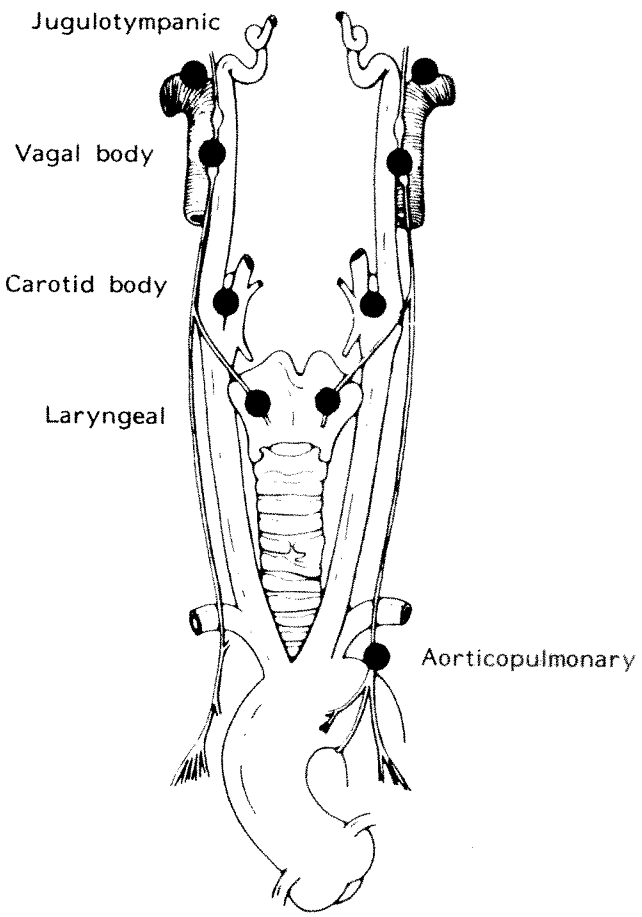

Figure 1 *Distribution of branchiomeric paragangliomas. Adapted from Lack* et al.[3]

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Table 1 *Clinical details of 25 patients with carotid body tumours and other cervical paragangliomas*

Sex (F:M)	16:9
Median age (years)	47
Range	17–61
Presentation	
Lump in neck	25
Hoarseness	2
Cranial nerve palsy of IX, X, and XIIth nerves	2
Hypertension	3
Previous operation	8
Previous radiotherapy	3
Diagnosis	
Biopsy	1
Angiography	24

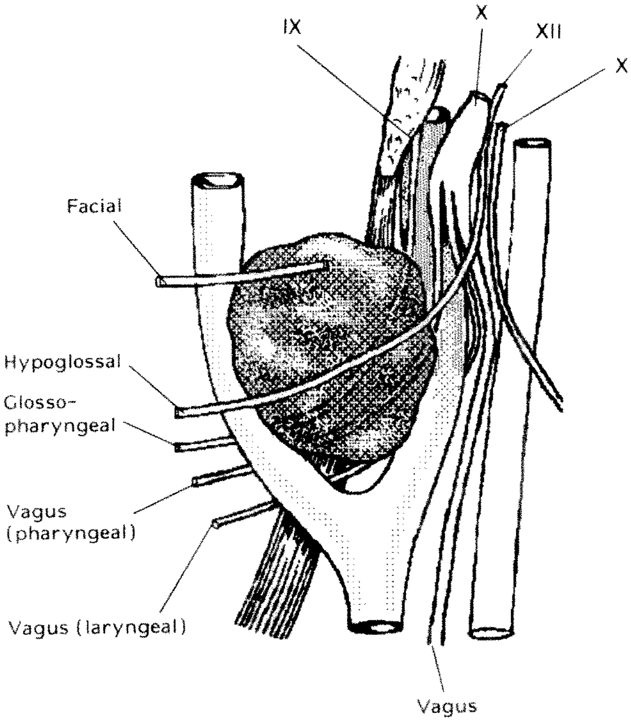

Figure 2 *Distribution of cranial nerves in relation to carotid body tumour emphasizing that the cranial nerves are at greatest risk during dissection of the upper pole and the back of the tumour*

Operative technique

Before surgery, patients are fully informed of the risks of hemiplegia and nerve damage. Patients are specifically asked for any history of dysphagia, hoarseness, difficult mastication and choking. Vocal cord movement is checked by indirect laryngoscopy. The operative approach is similar for all patients. A nasal endotracheal tube is inserted to facilitate access to the top of the tumour by having the mouth completely closed. With the patient supine and slightly flexed and the head rotated to the other side an incision is made along the length of the anterior border of the sternomastoid. Bipolar cautery is used to reduce the risk of nerve damage. Before attempting to remove the tumour it is essential to gain early control of the carotid arteries proximal and distal to the tumour using slings. It is important to identify the vagus and hypoglossal nerves as these may be adherent or even invaded by tumour. It is then possible to identify a cleavage plane between the carotid artery and the tumour within the adventitia, known as the 'White Line of Gordon Taylor'[9]. We advise starting the dissection at the bifurcation of the carotid artery and then proceeding towards the difficult area at the upper end of the tumour where there are a number of cranial nerves to be found (*Figure 2*). This plane is not always present and if there is invasion of the internal carotid artery or the common carotid artery it is necessary to insert a carotid artery shunt, resect carotid artery with the tumour and reconstruct the artery with an interposition vein graft. Usually, however, it is possible to peel the tumour off the internal carotid artery. This is a highly vascular tumour and the blood loss may be considerable. For the tumour that extends towards the base of the skull it may be necessary to mobilize the parotid gland, divide the digastric and stylohyoid muscles and the styloid process[12,13]. At the end of the operation a suction drain should be inserted and the wound closed in layers with catgut and Prolene® (Ethicon Ltd., UK).

Results

The results are given in detail in *Table 2*.

All patients presented with a lump in the neck of some duration, median 3 years (range from 2 months to 30 years). Two patients presented with cranial nerve palsies of the IX, X and XIIth nerves and two patients had hoarseness due to recurrent laryngeal nerve palsies. In three there was hypertension associated with raised vanillyl mandelic acid levels in the urine. In all but one patient who underwent a difficult biopsy before referral, the diagnosis was confirmed on angiography which showed a characteristic tumour blush in the carotid bifurcation. This procedure was not without risk: two patients had suffered a hemiparesis following carotid stab angiography before referral. It is our current practice to perform angiography using intravenous digital subtraction angiography (DSA) and this procedure was performed satisfactorily in four patients without complication (*Figure 3*). The most striking aspect of presentation was that in eight patients operative removal was attempted before diagnosis: two patients underwent an unnecessary and hazardous parotidectomy, and five had biopsy or attempted biopsy of a putative 'node'. DSA is a simple and safe investigation which will give accurate information, preventing unplanned and dangerous operations. Duplex Doppler imaging was used to diagnose a carotid tumour in one patient in this series, correctly identifying the site of the tumour between the carotid arteries and also the vascular nature of the tumour.

Using selective venous sampling of functionally active tumours two patients were found to have mediastinal paragangliomas, one at the hilum of the left lung and the other within the pericardium. Both were successfully removed. One further patient aged 17 years had had bilateral adrenal phaeochromocytoma and a para-aortic phaeochromocytoma resected before referral for removal of her carotid body tumour. Of the 25 patients, 22 underwent successful resection of carotid body tumours and a further three had excision of vagal paraganglioma. Three patients did not undergo operation as the first line of treatment but received radiotherapy. The tumours shrank

Table 2 *Outcome in the 25 patients with carotid body tumours and other cervical paragangliomas*

Operations	
Resections	26
Interposition vein graft	2
Embolization before surgery	2
No treatment	1
Carotid ligation	0
Mortality following operation	0
Morbidity following operation	
Hemiplegia	0
Cranial nerve palsy	8*
Pathology	
Single carotid body tumours	20
Bilateral carotid body tumours	2
Vagal chemodectomas	3
Associated functioning paragangliomas	5 (3 patients)
Local invasion of neighbouring tissues	7
Lymph node involvement	2
Follow-up period	
Median	3 years
Range	1 month–13 years
Recurrence	1

* Four patients had preoperative cranial nerve palsy and in seven the nerve was involved by malignant tumour

initially and then enlarged. In two of these it was possible to resect the tumour but in the third patient CT scanning showed intracranial extension.

Two days before resection two patients underwent embolization of their carotid body tumour using selective embolization of branches of the external carotid artery. These tumours had been previously explored elsewhere. It was difficult at definitive operation to assess whether embolization had reduced the vascularization of the tumour. Indeed in both tumours part of the blood supply arose from the internal carotid artery.

Of the 26 paragangliomas which were resected two required insertion of shunts. In both these patients resection of the internal carotid artery with replacement by an interposition saphenous vein graft was necessary. In one of these patients tumour was identified in the lumen of the artery.

Postoperative hemiplegia did not occur but there was transient cranial nerve weakness in two patients. In seven patients there was local invasion of the nerve by the paraganglioma, and the involved portion was resected with the tumour. Four of these (16 per cent) had obvious cranial nerve palsy before operation and a further three had vagal paragangliomas. The eighth patient had a large tumour and had undergone a previous attempt at removal. This was the only patient with cranial nerve damage attributable to operation (4 per cent). Histological proof of invasion of local structures, including nerve, artery and sternomastoid muscle, was obtained in these seven patients. Lymph node involvement occurred in only two patients out of 11 who had lymph nodes included in the specimen.

During the postoperative follow-up period (up to 13 years) only one patient undergoing resection has developed recurrent tumour. This patient died of neck and chest secondaries 3 years after resection.

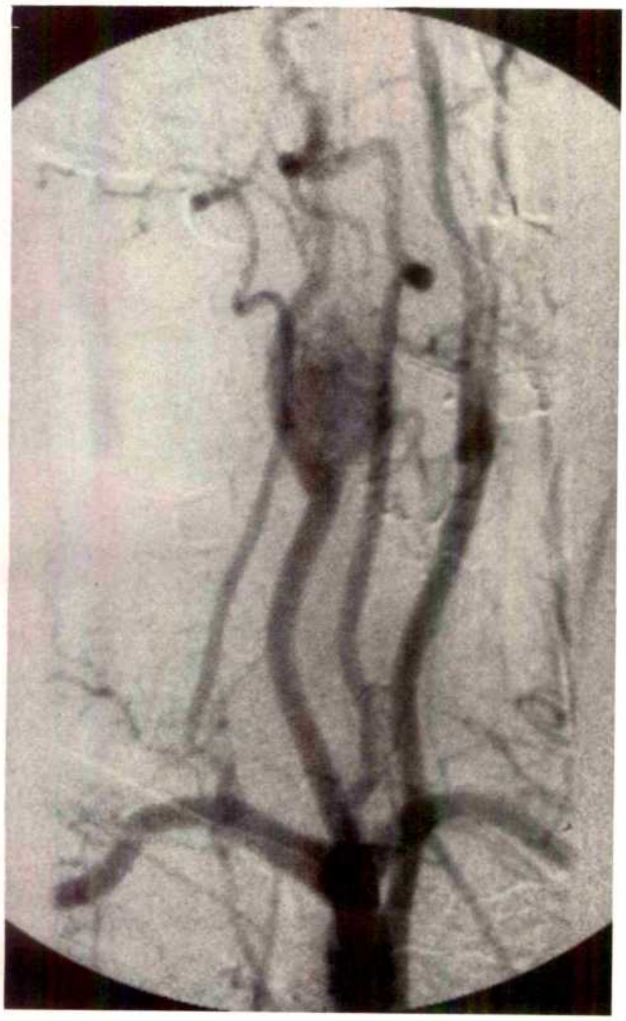

Figure 3 *Intravenous digital subtraction angiogram showing carotid body tumour at the bifurcation of the right carotid artery*

Discussion

This series illustrates several important points. First, at presentation the tumours may be multiple and associated with secreting paragangliomas elsewhere in the body. Secondly, it is now possible to diagnose carotid body tumours without angiography, and the diagnosis should now be made using the safer investigations of intravenous DSA, technetium scanning or duplex Doppler imaging. These are not hazardous and are much preferred to unplanned surgical exploration. Duplex scanning and technetium isotope scanning are entirely non-invasive methods and are suitable for establishing the diagnosis. DSA will provide an accurate plan of the tumour blood supply which is available for reference in the operating theatre. If the diagnosis is not suspected until operation the tumour must not be biopsied as this carries a high risk of stroke. The best policy is to close the wound and replan the procedure electively. If the upper limit of the tumour cannot easily be felt a computerized tomography (CT) scan should be performed to assess intracranial extension. Indeed, perhaps the most useful classification of carotid body tumours is into those with and those without previous surgery and those with and those without intracranial extension.

Preoperatively, two patients in this series had hoarseness and a lump in the neck and two others had definite cranial nerve palsies. In such patients a combined approach is necessary and should include ENT assessment of the pharynx, larynx and lower cranial nerves as well as angiographic assessment of the extent of vascular involvement. At operation, particularly for large tumours, a dual approach by vascular and ENT surgeons is recommended.

The major series of carotid body tumours reported in the last 20 years are listed in *Table 3*. Resection of carotid body tumours is associated with a mortality rate of up to 10 per cent[8], a hemiplegia rate of up to 20 per cent[8] and a cranial nerve damage rate of around 50 per cent in some series[15]. This series has a zero

Table 3 *Cervical paraganglioma: outcome of major recent series*

Centre	Year	No. resected	Mortality	Hemiplegia	Cranial nerve palsy	
					No. of patients	%
Westminster[14]	1965	8	1	1		
Mayo[8]	1971	58	4	5	14	24
Houston[15]	1972	18	0		10	56
Cleveland[16]	1978	31	1		17	55
Toronto[17]	1981	23	1		8	35
San Francisco[18]	1982	15	0		7	47
Johannesburg[19]	1986	46	2	1	8	17
Mayo[20]	1988	29	0	1	15	52
St. Mary's/Hammersmith (present study)	1988	26	0	0	8	31

mortality and a zero hemiplegia rate. Cranial nerve involvement was found in 31 per cent of tumours resected. Only one patient (4 per cent) had damage to a normal cranial nerve despite a high resection rate of 96 per cent and he had had a previous attempt at removal. This series compares well with a recent report from the Mayo Clinic[20] of 153 carotid body tumours collected over 50 years. While their mortality and stroke rates have fallen the postoperative cranial nerve dysfunction rate remains unchanged at 40 per cent[20], and tends to be higher with larger tumours. Mayo Clinic workers found that the principal area of damage was in dissection of the upper end of the tumour and this is partly due to direct tumour invasion. It is possible that earlier resection may reduce the risk of cranial nerve involvement.

The technical aspects of resection have already been outlined but some points require emphasis. First, preoperative assessment should include careful pharyngoscopy as the tumour may extend into the pharynx or larynx. At least 6 units of blood should be cross-matched for the operation. At operation early control of the carotid vessels must be obtained with sacrifice of the external carotid artery if necessary. The tumour will often push the external carotid artery anteriorly. There is now no place for carotid artery ligation although division of the external carotid artery is often a useful manoeuvre to mobilize the tumour. The indication for insertion of a shunt is full-thickness invasion of the carotid artery by tumour or inadvertent damage to the carotid artery during dissection. The surgeon must be competent at insertion of carotid shunts and interposition vein grafting and thus ideally should be a vascular surgeon experienced in carotid artery surgery. Routine shunting is not necessary but a shunt should be readily available for every operation. Resection with complete rather than partial excision should be the aim of every operation. For patients with bilateral tumours the approach should be staged into two operations because of the risk of bilateral vocal cord palsy and between the two operations the vocal cords should be checked.

Postoperatively the patient should be managed in a high dependency unit in the prone position with monitoring of the blood pressure and neurological status. The patient should not drink any fluids until fully conscious. A doctor must be in attendance at the first drink as the patient may aspirate in the presence of cranial nerve damage.

The experience of this series suggests that while the tumour is often locally malignant (30 per cent of patients) lymph node involvement only occurred in 8 per cent of patients. This is in contrast to the South African series from Witz University where there was a 20 per cent incidence of lymph node involvement[19]. It is likely that metastasis is a late event. Martin *et al.* (1973)[7] reported on the natural history of 28 patients with carotid body tumours who received no treatment. Observed over a mean period of 11 years, seven developed node metastases and two died of distant metastases.

There are only two other treatment options: embolization and radiotherapy. Radiotherapy has been reported to have a high success rate with disappearance of the tumour in nine of 12 patients[21]. However, in three of our patients these tumours recurred after a short period of time, presenting a formidable operative risk; two were resectable, one had intracranial tumour extension and no treatment was possible. Embolization has been reported as a useful preoperative manoeuvre[22] and was used in two of our patients but did not significantly reduce the operative bleeding as the tumour received a blood supply from the internal carotid artery. It also carries a risk of hemiplegia and we have now abandoned this procedure except for large technically difficult tumours where there has been previous surgery. As palliative treatment of an unresectable tumour, embolization may have a useful role.

In conclusion, carotid body tumours form only part of a complex pattern of paragangliomas, some of which may secrete catecholamines[23]. These tumours may be diagnosed by the relatively safe method of intravenous DSA and duplex Doppler scanning. As these tumours are locally malignant, resection offers a chance of cure particularly if performed when the tumour is small. However, resection may require the insertion of a carotid shunt during the operation and for large or complicated tumours a combined team of ENT and vascular surgeons is preferable. Following successful resection the outlook is good and tumour recurrence is uncommon.

Acknowledgements

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Viscoelastic properties and collagen content of the long saphenous vein in normal and varicose veins

Veins taken from patients undergoing surgery for varicose veins were compared with those obtained from patients undergoing other surgical procedures ('normals'). Varicose veins had a lower breaking strength and breaking energy than normal veins. Elastic stiffness was less in normals ($\tan\theta = 41$ (24)) than in varicose veins ($\tan\theta = 55$ (18); $P<0{\cdot}01$). There was no difference in viscoelastic behaviour between samples taken above, at, or below the valve leaflet insertion. In normals, perivalvular vein wall exhibited a 50 per cent lower breaking strength and elastic stiffness than vein from other sites. Collagen content was significantly higher in normal vein specimens in all sites examined (mean collagen content = 70 (21) μg/mg, versus *51 (20) μg/mg for varicose veins; $P<0{\cdot}001$). We conclude that significant structural changes are seen in varicose veins. In normal veins, the perivalvular vein wall has distinct viscoelastic features when compared with vein wall from other sites. This difference was not found in veins which became varicose.*

Keywords: Varicose veins, long saphenous vein, viscoelasticity, collagen, venous valves

J. V. Psaila and
J. Melhuish

University Department of Surgery,
University of Wales College of
Medicine, Heath Park,
Cardiff CF4 4XN, UK
Correspondence to:
Mr J. V. Psaila

It has long been recognized that valvular incompetence is invariably present in patients with varicose veins. This defect permits reverse flow in the diseased veins and an abnormal outward and retrograde flow of blood from the deep system to the superficial veins following muscular exertion. In 1603 the anatomist Heironymous Fabricius of Aquapendendente wrote that valves were created by nature to ensure a 'fair general distribution of the blood'[1]. The special role of valves in counteracting the consequences of muscular activity on venous return, rather than acting as antigravity devices, is now universally acknowledged.

In this study we have analysed the viscoelastic properties and collagen content of varicose and normal veins. We have tried to identify a locus in the vein wall adjacent to the venous valves which could become dilated or varicose and render the vein incompetent.

Materials and methods

Fresh samples of the long saphenous vein were obtained from patients undergoing surgery for extensive thigh block dissection (usually melanoma) or from graft procedures or amputated limbs. Varicose veins were taken from vein stripping procedures using a Babcock stripper. The entire vein was dissected open, longitudinally pinned out and measured, and the number of valves counted. Using a preset cutter, 3-mm samples were cut circumferentially from segments of the long saphenous vein, at the thigh, near the knee and near the ankle. Vein wall sections immediately adjacent to the valve leaflet insertion ('perivalvular vein wall') were studied in greater detail, and 3-mm samples taken from just 'above', 'at' and immediately 'below' the valve leaflet site. Samples above and below the valve were carefully taken to exclude any valve tissue. Significant variceal dilatations or sacculations, when present, were also sampled and analysed separately.

Viscoelastic studies

The excised samples were first mounted in an extensiometer (constructed in the Department of Surgery, University of Wales College of Medicine) which features two serrated-toothed clamps set 3 mm apart at zero tension. The tissue was kept moist at all times in cool Ringer's solution buffered to pH 7·4 and sandwiched with a piece of filter paper between the jaws of the two clamps, to avoid crushing and disruption at the attachment points. The specimen was disrupted by the progressive separation of the jaws, driven at 3·1 mm/min, and thereby subjected to a constant deformation rate. The load-deformation viscoelastic curve was processed by strain gauge force transducers connected to a Wheatstone bridge. The output was displayed on a chart recorder (chart speed: 31 mm/min) via an instrumentation amplifier. From the several measurements provided by the deformation curve (*Figure 1*), three were examined in detail[2]:

Breaking strength. F_{max} is the force or load required to disrupt the vein wall, expressed as the load in grams per unit cross-sectional area in millimetres squared (g/mm^2).

Breaking energy. The total energy required to disrupt the specimen obtained from the area of the viscoelastic curve up to breaking point,

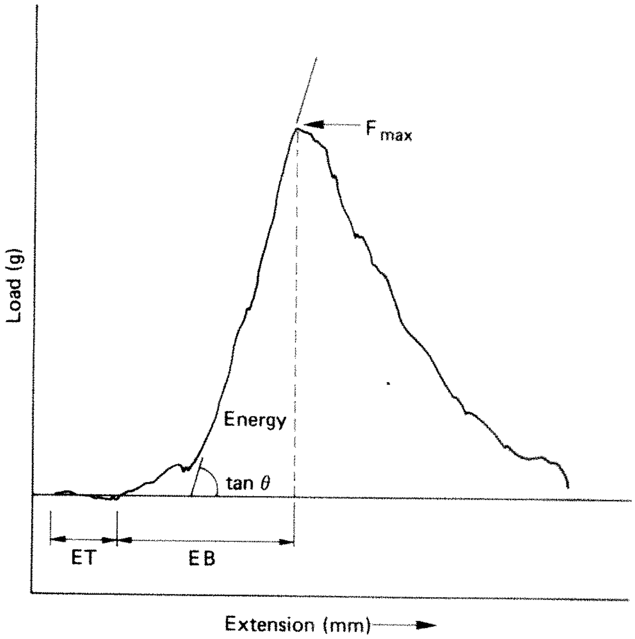

Figure 1 *A typical viscoelastic curve for (varicose) vein wall. ET, extension to take-off; EB, extension to breakage; F_{max}, load required to achieve breakage or breaking strength; energy, total energy required to break the specimen (area of curve to breaking point); tan θ, elastic stiffness*

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Table 1 *Viscoelastic properties of varicose and normal veins*

	Normals	Varicose veins
Wall thickness (mm)	1·18 (0·4) $n = 50$	1·48 (0·4) $n = 27$
Breaking strength (F_{max}, g/mm^2)	97 (100)† $n = 50$	49 (28) $n = 26$
Breaking energy (mm^2/mm^3)	47 (59)† $n = 50$	19 (7) $n = 27$
Elastic stiffness (tan θ)	41 (24) $n = 50$	55 (18)* $n = 27$

Values are means with s.d. in parentheses; * $P < 0·01$; † $P < 0·005$ (normals *versus* varicose veins)

Table 2 *Viscoelastic characteristics of the long saphenous vein according to anatomical site*

	Breaking strength (g/mm^2)	Breaking energy (mm^2/mm^3)	Elastic stiffness (tan θ)
Thigh	110 (71) $n = 42$	76 (45) $n = 44$	59 (21) $n = 39$
Knee	74 (48) $n = 19$	24 (14)* $n = 17$	60 (20) $n = 18$
Ankle	50 (30)† $n = 16$	14 (5)† $n = 15$	58 (17) $n = 17$

Values are mean with s.d. in parentheses; † $P < 0·001$ (thigh *versus* ankle); * $P < 0·01$ (thigh *versus* knee)

and expressed as area in millimetres squared per unit of tissue volume in millimetres cubed (mm^2/mm^3).

Elastic stiffness. The deformation rate was obtained from the linear part of the curve and measured in degrees as the tangent of the angle α (tan θ).

The thickness of the vein sample was measured at room temperature by means of an optical micrometer, while assembled in the tensiometer jaws at zero tension.

Collagen estimation. The vein samples used for tensiometry were weighed and kept frozen at −70°C. Previous work has shown that collagen content did not change in samples stored for up to 3 weeks. Hydroxyprolene content was determined by Woessner's assay[3], this amino acid being almost exclusively present in collagen. Hydroxyprolene content was expressed as micrograms per milligram of wet weight of tissue.

Statistics

All values were fed into a computer file (Honeywell DPS-8/70 Waltham, Massachusetts, USA) and analysed by a Minitab package (release 513). Data values were read in columns and the variables extensively plotted (scattergrams) for any positive correlation or significant sex or age differences. Histograms were constructed to ascertain data distribution, skewness, and kurtosis. Statistical significance was tested by the two-sample Student's t test, and P values $< 0·05$ were taken as indicating significant differences. All results are expressed as the mean and standard deviation (s.d.). Data which were not normally distributed were analysed by the Mann–Whitney U test.

Results

The results of a typical strain-deformation curve are shown in *Figure 1*. In the slow initial extension phase the vein exhibited plastic behaviour and the curve was relatively linear, facilitating calculation of the slope angle or elastic stiffness (tan θ).

Macroscopic features

An average of 3·6 (1·9) valves were found in the long saphenous vein sample taken from patients with varicose veins, with a higher proportion of valves found in the proximal (thigh) vein (average 2·0 (1·4), $n = 36$) than distally in vein from the knee or leg (average 0·8 (0·7), $n = 26$ and 0·7 (0·6), $n = 21$ respectively). Patients with normal veins showed no significant difference in overall valve frequency, with an average of one valve every 11·4 cm, compared with every 12·8 cm in varicose vein patients.

Average vein wall thickness was slightly greater at the knee (1·61 (0·6) mm) than at the thigh (1·37 (0·5) mm) or ankle (1·39 (0·5) mm, $n = 14$), both in normals and patients with varicose veins.

Sacculations or local dilatations ('blow outs') of the vein wall were infrequently seen, being present in only 33 per cent of veins. These were closely associated with valve cusps, but not sited preferentially above or below the valve leaflets, being found more frequently in the thigh (average 0·5, $n = 32$) than in knee (average 0·3, $n = 26$) or leg (average 0·15, $n = 26$) samples of vein.

Viscoelastic behaviour

Breaking strength and breaking energy were significantly greater in normal veins but varicose veins showed a higher elastic stiffness (*Table 1*).

In both normal and varicose vein patients, vein taken from the ankle had a significantly lower breaking strength than thigh or knee vein (*Table 2*). Similarly, breaking energy was found to be highest at the thigh and least at the ankle. Elastic stiffness did not alter significantly for any of the three sites examined.

Vein wall characteristics adjacent to the valves

At the three sites immediately adjacent to the valve cusps, i.e. just above, at and below the valve leaflet, there was no difference in vein wall thickness, breaking strength, breaking energy or elastic stiffness (*Figure 2*). This finding was confirmed both in normal veins and in samples taken from patients with varicose veins.

On comparing vein wall samples taken adjacent to the valve leaflet site with those obtained from other parts of the vein, no significant difference in viscoelastic behaviour was found in patients with varicose veins. In normals, however, there was a significant difference in breaking strength, with a 50 per cent reduction in tensile parameters at the perivalvular vein wall. Similarly, elastic stiffness was markedly lower in vein wall adjacent to the valve leaflet than at other sites (*Table 3*).

Collagen content

Samples of vein taken from patients with varicose veins yielded a lower average hydroxyprolene content than those taken from normal patients (normals, 70 (21) μg/ml wet weight, $n = 43$ and varicose veins, 51 (20) μg/mg, $n = 42$; $P < 0·001$). The difference between these two groups was observed in all sites examined, including samples taken above, at or below the valve cusps (*Figure 3*).

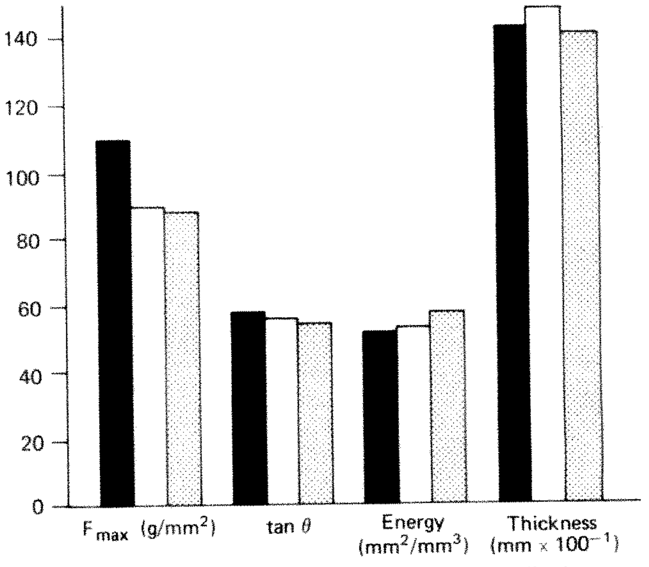

Figure 2 *The viscoelastic characteristics of the vein wall adjacent to the valve leaflet. Data from both varicose vein and normal samples from below-knee samples* (n = 26). ■, *Above valve leaflet;* □, *at valve leaflet;* ▨, *below valve leaflet*

Table 3 *Viscoelastic behaviour of the vein wall in relation to valve leaflets, analysed separately for normals and varicose veins*

	Normals		Varicose veins	
	Peri-valvular	Other sites	Peri-valvular	Other sites
Breaking strength	61 (63)	134 (132)*	50 (21)	50 (33)
(g/mm²)	$n = 27$	$n = 23$	$n = 11$	$n = 17$
Breaking energy	35 (10)	59 (65)	21 (7)	18 (7)
(mm²/mm³)	$n = 27$	$n = 23$	$n = 11$	$n = 15$
Elastic stiffness	31 (4)	52 (22)†	56 (16)	53 (21)
(tan θ)	$n = 27$	$n = 23$	$n = 11$	$n = 16$

Values are means with s.d. in parentheses; * $P < 0{\cdot}02$; † $P < 0{\cdot}01$ (other sites *versus* perivalvular)

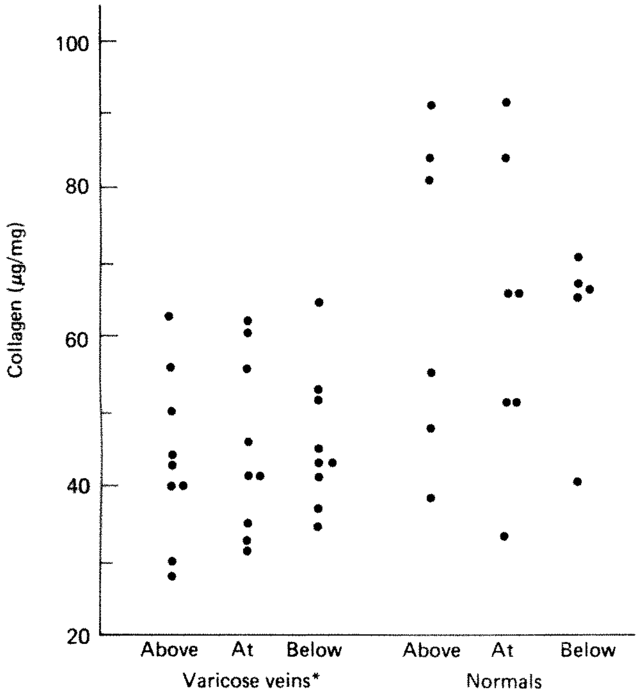

Figure 3 *The collagen content of the long saphenous vein in normals and in those with varicose veins, analysed from three sites at or adjacent to the valve leaflet insertion* (* P < 0·001, *varicose veins* versus *normals*)

Discussion

Brodie[1] in 1900 defined a 'varicose' vein (from Latin *varus* for 'bent or crooked'[4]) as one which is 'unnaturally dilated'. Many authors have since observed that varicosities tend to develop within the tributaries or stem branches of the long saphenous vein[5,6] and are often limited to the thigh[7] or found only below the knee[6]. In his thesis, Cotton[6] summarized three distinct features of varicose veins: (1) a localized dilatation or sacculation (termed a 'varix') found below the valve leaflet; (2) a simple cylindrical dilatation of the vein or 'aneurysm' formation; (3) a serpentine or 'spiral' elongation of the smaller tributaries. Histological examination of the vein reveals, even at an early stage, widespread muscle hypertrophy and disruption of the elastic lamina[6]. Fibrosis and other focal changes are subsequently seen within the muscle cells, but these are not uniformly found throughout the vein wall[6–10]. The elastic lamina may degenerate and become indistinct. Recent studies of the vein wall using light and electron microscopy reveal an abnormality of the muscle cell associated with collagen infiltration[10].

We frequently observed dilatation of the saphenous vein but were unable to quantify this in excised specimens. The commonest and most striking change of discrete unilateral sacculations[11] was randomly found at the level of the valve cusps, but always closely associated with the leaflet insertion site. Our stress studies comparing three sites, above, at, or below the valve cusps, failed to identify a specific portion of the vein wall which was prone to develop structural weakness, both in normals and in patients with established varicose veins (any sacculations we tested were structurally weaker and less elastic than normal vein wall). The vein wall surrounding these localized dilatations is reported to show intact tissue layers on histological examination[6].

In varicose veins the vein wall becomes attenuated at the valve sinus, with effacement of the 'commissural mound' in between the valve cusps (the 'agger'), presuming a pre-existing locus of wall weakness[10]. A pre-existing structural defect close to the valve leaflet has not been previously identified[12,13], and is confirmed in our studies on normal vein. The difference in structural behaviour between perivalvular vein wall and other parts of the vein wall was not present in established varicose veins, reflecting the pathological changes within the tissue layers[6,9]. In a similar study comparing the tensile strength of the actual valve leaflet with valve wall within the femoral vein, the valve cusps were found to be slightly stronger than adjacent vein wall[13].

There is wide variation in the reported number of valves present in the long saphenous vein, ranging from zero to 20[5,6,13–19]. Few authors have compared normal with varicose veins, with no published phlebographic studies documenting the number of functional valves[19], although it has recently been suggested that the sinusoidal 'bulges' seen radiologically correlate poorly with the presence of valves[16]. We were impressed by the low incidence of venous valves within the long saphenous trunk, both in normals and in varicose vein patients.

The collagen content of vein samples taken from normal patients was higher, in our study, than for varicose vein patients. This difference is unlikely to be a localized or chance finding, as it was consistently found at all three sites examined adjacent to the valve insertion, and has been confirmed by other authors[20]. It may reflect the morphological changes seen in varicose veins, which are known to contain a higher proportion of muscle cells[6,10] and show fatty infiltration in the vein wall[21].

It has been argued that a generalized distensibility of the vein wall results in secondary incompetence of the valve cusps[22]. Various valve defects have been reported, including congenital valve absence[23], an evagination or herniation at the commissures[11], adhesions, bulging and endothelial irregularities which may inhibit valve function[17], and a 'valvulitis'[24]. Architectural valve changes have been observed in animal models subject to venous hypertension[25]. Arteriovenous fistulae may play a role in the formation of varicose veins[26]. From our studies, it appears that changes in perivalvular vein wall structural behaviour are accompanied by an overall reduction in collagen content. These may result from an enzyme defect affecting the biosynthesis of a genetic collagen type (as postulated for arterial aneurysm formation[27,28]). Indeed, as also reported by others[29], we have observed varicose vein formation in a patient with localized Ehlers–Danlos syndrome below the knee (unpublished findings). The functional significance of the diverse collagen types found in vascular tissue is not fully understood[28], and may yet prove to be relevant in understanding the causation of varicose veins.

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^{111}In-labelled leucocyte imaging in vascular graft infection

D. C. Berridge, J. J. Earnshaw, M. Frier*, A. C. Perkins*, M. L. Wastie†, B. R. Hopkinson and G. S. Makin

*Departments of Vascular Surgery, *Medical Physics and †Radiology University Hospital, Nottingham, UK*

Correspondence to:
Mr D. C. Berridge

Twelve patients with a clinical diagnosis of possible vascular graft infection have been studied over the last 3 years. All patients had their leucocytes labelled with indium-111 and γ-camera imaging after 24 and 48 h. Subsequent management was according to established surgical techniques. Eight patients proved to have vascular graft infection and indium uptake was seen along the length of the graft in six. Two patients with open wound infections and synthetic grafts had localized uptake only on leucocyte scanning. Four patients, all of whom had negative scans were not thought to have infected grafts after further investigation using digital subtraction angiography and computed tomography scanning. These patients have been followed up for a median period of 19 months (range 5–25 months) and have remained symptom free. Initial experience with ^{111}In-labelled leucocyte scanning has been encouraging, both in diagnosis and in planning the management of patients with graft infections.

Keywords: ^{111}In-labelled leucocytes, vascular graft infection

Vascular surgery has always been regarded as being relatively 'clean' surgery, especially in the elective or non-trauma patient. However, infection of a prosthetic graft occurs in up to 6 per cent of patients undergoing vascular reconstruction, and is associated with high mortality and morbidity rates[1–3]. In the early stages it can be difficult to distinguish between a superficial wound infection and a localized graft infection. Various modalities[4–6] have been used to attempt to improve the diagnosis of graft infection with the hope that earlier diagnosis will allow early aggressive local treatment.

Therefore, we have undertaken an evaluation of ^{111}In-labelled leucocyte imaging in patients with a clinical diagnosis of possible vascular graft infection. The management of these patients was not altered by the result of the radionuclide scan to allow the eventual clinical outcome to be correlated with the radionuclide scan findings.

Patients and methods

Patients

Over the last 3 years (1985–1987), 12 patients with a clinical diagnosis of possible graft infection have been evaluated with ^{111}In-labelled leucocyte scintigraphy. They were predominantly male patients (11:1) with a mean age of 62·4 ± 8·7 years. Indicators of possible graft infection included persistent pyrexia or leucocytosis, persistent wound discharge with positive culture, infected false aneurysms, graft tenderness, and/or general malaise or abdominal pain in the absence of other identifiable pathology.

Methods

Labelling of leucocytes with ^{111}In-oxine

A sample of 17·5 ml of the patient's blood was placed in a plastic tube (20 ml) (Sterilin Ltd., Feltham, UK) containing 3·5 ml of acid/citrate/dextrose (ACD) solution and gently mixed. This tube was then incubated at 37°C for approximately 45 min to sediment the erythrocytes.

Using a slightly modified method of Peters *et al.*[7], a mixed leucocyte ^{111}In-oxine labelling was performed in saline/ACD, but the period out of contact with plasma was kept as short as possible. Five millilitres of the cell-free plasma was added, mixed by gentle inversion and then centrifuged at 900 r.p.m. for 10 min. The supernatant was then discarded.

The leucocyte pellet obtained was resuspended in a further 5 ml of cell-free plasma and the preparation was finally assayed for activity.

Cell-free plasma was obtained by centrifuging the platelet rich plasma at 2400 r.p.m. for 10 min. The supernatant cell-free plasma was removed and stored at 37°C until required.

Actual activity injected was approximately 10 – 11 MBq.

Imaging was performed at 24 h and 48 h on an IGE 400T γ-camera fitted with a medium energy collimator and using both peaks of indium-111.

Results

There were no complications associated with the technique in any of the patients studied. The median period to presentation was 10 weeks (range, from 2 weeks to 4 years). Of the 12 patients studied, there were four negative scans, two with only localized uptake and six with either multifocal or full-length uptake.

Negative ^{111}In-labelled leucocyte images (Table 1)

The usual presenting feature was a pyrexia associated with abdominal pain and general malaise. Spontaneous improvement was seen in three patients and a urinary tract infection was confirmed on subsequent culture in the fourth patient. In one patient a resolving non-infected haematoma was monitored with serial computed tomography (CAT) scans.

Positive ^{111}In-labelled images

Localized uptake (Table 1). Both patients had a persistent groin discharge with culture of *Staphylococcus aureus*. Appropriate intensive intravenous, local gentamicin beads and subsequent oral antibiotic therapy cleared the infection in the latter patient, with a patent graft remaining at 14 months. The other patient failed to respond and required graft excision and a subsequent Gritti–Stokes amputation. At operation (a month after imaging) the entire length of the graft had become infected—he died after a stroke 8 months later.

Full-length or multifocal uptake (Table 2). All six patients had highly positive images (*Figure 1*) and positive cultures from either a discharging wound or sinus. *Staphylococcus aureus* was found in all cultures, and *Streptococcus* sp. was also found in one case. Five (83 per cent) had had multiple vascular procedures performed over a period of up to 7 years. Two patients required a below-knee amputation following occlusion of the graft and

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Table 1 *The ^{111}In-labelled leucocyte images in those with negative images and those with a localized positive image*

Site	Graft	Presentation	Outcome
Negative images			
Femorofemoral	Dacron	Pyrexia of unknown origin	Subsequent recultures: urinary infection
Aortic	Dacron	Persistent pyrexia postoperatively	Settled spontaneously
Aortic	Dacron	Pyrexia, abdominal pain, malaise	Computed tomography scan negative, settled spontaneously
Aortic	Dacron	Pyrexia, abdominal pain, malaise	Computed tomography scan negative, settled spontaneously
Localized positive images			
Femoropopliteal	PTFE	Wound dehiscence, infection	Failed antibiotic therapy, Gritti–Stokes amputation
Aortobifemoral	Dacron	Persistent groin discharge: positive culture	Successful antibiotic therapy

PTFE, polytetrafluoroethylene

Table 2 *Positive ^{111}In-labelled leucocyte images: full length or multifocal uptake*

Site	Graft	Presentation	Outcome
Femorofemoral	Dacron	Persistent groin discharge (*Staphylococcus aureus*/*Streptococcus* sp.)	Graft excision, below-knee amputation
Femorofemoral	Dacron	Persistent sinus, bilateral false aneurysms, haemorrhage (*S. aureus*)	Graft excision, early rethrombosis of autogenous reconstruction
Axillofemoral Femoropopliteal	Dacron PTFE	Persistent stump discharge (*S. aureus*) Groin swelling (*S. aureus*)	Femoropopliteal graft excision, all wounds healed
Femoropopliteal	PTFE	Septicaemia, popliteal discharge (*S. aureus*)	Graft excision, drainage of metastatic abscess, above-knee amputation
Axillofemoral	Dacron	Slow healing groin wound (*S. aureus*)	Graft excision, above-knee amputation
Femorofemoral Femoropopliteal	Dacron PTFE	Groin abscess (*S. aureus*)	All grafts excised

PTFE, polytetrafluoroethylene

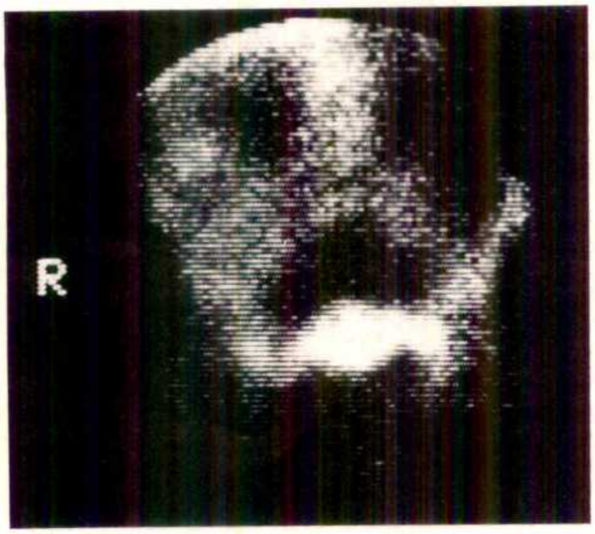

Figure 1 *^{111}In-labelled leucocyte scan showing full-length uptake in a Dacron femorofemoral crossover graft*

before any recognition of graft infection. All patients failed to respond to intensive antibiotic therapy in association with graft drainage. Subsequent to graft excision, amputation was necessary in a further three patients (50 per cent). An asymptomatic metastatic chest wall abscess was detected in one patient and was subsequently drained (*Figure 2*). Differential uptake clearly separated an infected femoropopliteal (polytetrafluoroethylene) graft, from an uninfected axillofemoral (Dacron®, E. I. Dupont de Nemour Inc.) graft in the same patient (*Figure 3*). There was no operative mortality; however, two patients died, one from a ruptured aortic aneurysm, and one from a stroke 8 months later. All wounds have healed in the survivors.

Median follow-up time for patients with negative or localized positive scans is now 19 months (range, 5–25 months).

Discussion

Most of the patients with positive images had undergone multiple vascular procedures over a variable period of time up to 7 years. It is therefore difficult to be certain when the infection commenced, as it is known that prosthetic grafts can become infected many years after the initial operation[8,9].

Although infections in the six patients with full-length or multifocal images were suspected clinically, the images obtained were distinct. Similarly, the four patients with negative scans have all failed to demonstrate any sign of graft sepsis on subsequent follow-up. It is, however, more difficult to be certain of the interpretation of a localized positive image. Serial imaging after antibiotic therapy and any necessary drainage procedure may help in these particular cases. The main advantage of this technique is in the detection of localized infection which may allow early localized treatment with reduction in morbidity and mortality.

False positives may occur; one reason is that platelet contamination inevitably occurs as a result of this mixed leucocyte labelling technique, although this was not the case in the present study. False positive images may be accounted for by uptake in accessory spleens, bowel, bladder, lung in cystic fibrosis[10], and also in both primary and secondary neoplasms[11]. False aneurysms have also been reported to cause false positives[12]. Thus the interpretation of these scans should be based on the clinical status of the patient and knowledge of the site of the grafts. Any unexplained positive images should be fully investigated using alternative techniques.

Other methods which have been used have disadvantages. Ultrasound and computed axial tomography scans may show a perigraft collection of fluid; this does not necessarily confirm infection. The presence of air bubbles in the perigraft fluid allows a more confident diagnosis on CAT scanning[4,13]. However, most common pathogens found in infected grafts are *S. aureus* and *Escherichia coli*., which do not produce gas[14]. Aspiration of perigraft fluid under ultrasound or CAT control can allow both confirmation of infection and determination of sensitivity[15], but is also subject to sampling error and has the increased risk of fatal haemorrhage in the presence of infection.

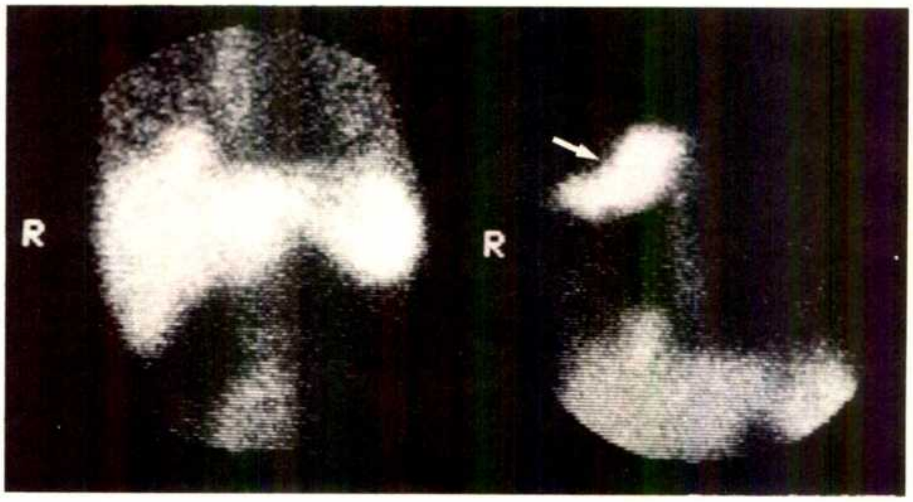

Figure 2 ^{111}*In-labelled leucocyte scan showing an occult chest wall metastatic wall abscess (arrowed)*

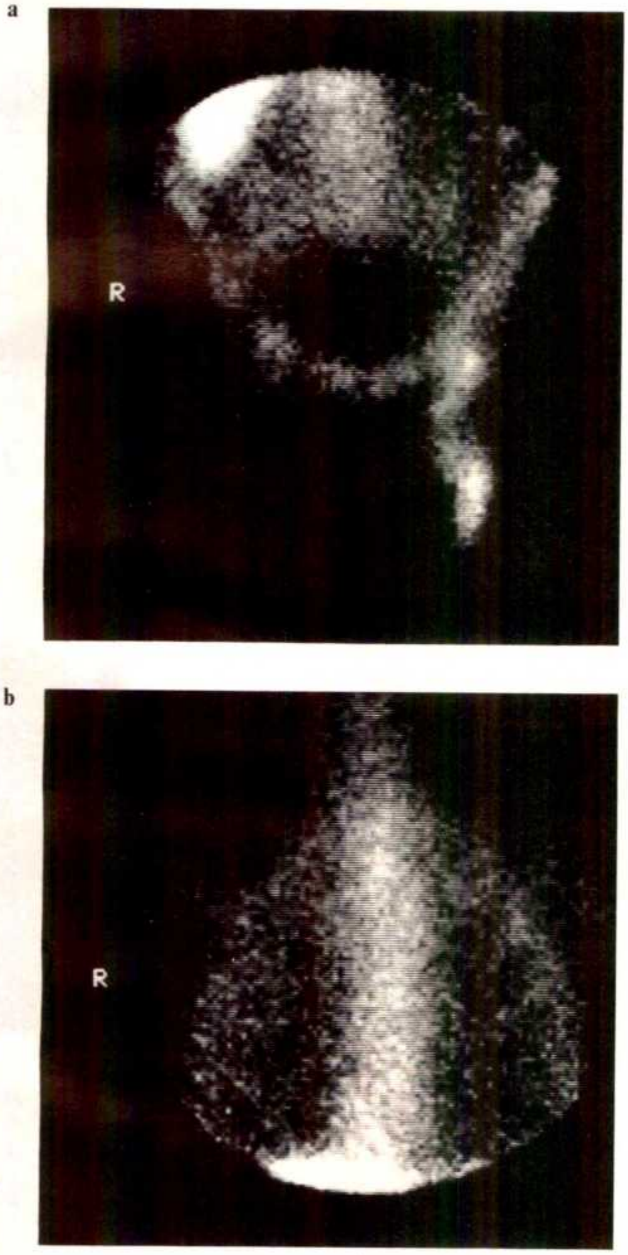

Figure 3 ^{111}*In-labelled leucocyte scan showing:* **a**, *multifocal and full-length uptake in a left femoropopliteal graft (polytetrafluoroethylene);* **b**, *(the same patient as* **a***) a left axillofemoral graft with no increased uptake*

Furthermore they do not reveal the extent of the infection. An opposite conclusion was reached by Mark *et al.*[13]; however, this was based on three cases where ^{111}In-labelled leucocytes had demonstrated groin infection but had not shown retroperitoneal infection. The CAT scan was considered positive after revealing perigraft fluid, but this is not specific to infection alone.

^{111}In-labelled leucocytes are preferred to gallium citrate, because the latter has a lower sensitivity and has a longer delay before imaging is possible[16]. Williamson *et al.*[17], using autologous ^{11}In-oxine-labelled leucocytes, found a sensitivity of 100 per cent, a specificity of 88 per cent, and an accuracy of 93 per cent. All scan positive patients were explored and infection confirmed. They also found that CAT scan evaluation was inferior; if fluid or gas was needed to identify graft infection then the sensitivity would be only 37 per cent. Similarly, antibiotic therapy[18] or the chronicity of infection[19] does not impair the sensitivity. Newer radiopharmaceuticals such as technetium-99m hexametazine (HM-PAO, Ceretec, Amersham International, Amersham, UK) appear promising and may allow quicker, higher definition images which may be of particular use in the aortic region. An additional advantage of ^{111}In-labelled leucocyte imaging, is that other sites of infection may also be revealed which might otherwise adversely affect the prognosis of that patient.

Radionuclide imaging of patients with grafts appears to offer a superior method of diagnosing graft sepsis but remains underused[20]. Patients with true positive scans have a significantly increased mortality[21]. The use of ^{111}In-labelled leucocytes in this study has proved helpful in clinical practice. This technique may allow detection and treatment of infection while it is still localized, and therefore may allow local treatment of infected prosthetic grafts[22] with reduction in morbidity and mortality. It has also been shown to allow the differential management of infected and uninfected grafts within the same patient.

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Risk factors in onychocryptosis

A study is described in which the normal toes of 50 patients with unilateral ingrowing toenails were compared with those of 50 healthy subjects matched for age and sex. Twenty-one potential risk factors were compared between the groups. All measurements on patients were derived from unaffected toes in order to avoid anatomical distortion due to the disease process. Statistical analysis revealed significant differences between the groups for three anatomical measures, namely nail fold width ($P<0{\cdot}001$)*, medial rotation (eversion) of the great toe* ($P<0{\cdot}02$) *and nail thickness* ($P<0{\cdot}03$)*. Possible discriminating variables were assessed using linear discriminant function analysis and a mathematical equation was derived based on these three factors. This equation was found to possess a potentially high predictive value in that it correctly classified 86 per cent of the patients and 77 per cent of the controls. A further group of 62 unselected patients presenting with unilateral onychocryptosis and 35 unaffected controls were assessed for these three parameters. Of these, 80 per cent of controls and 85 per cent of patients could be classified correctly by the equation. It is thus proposed that, in the majority of subjects with onychocryptosis, a discrete anatomical predisposition exists and that the other factors act only as triggers in the development of the condition. This study provides a rationale for less traumatic surgical approaches to ingrown nail than nail avulsion, with or without nail bed ablation and may also provide a means of identifying high-risk groups.*

Keywords: Onychocryptosis, risk factors, controlled study

D. T. Langford,
C. Burke and
K. Robertson*

Wellcome Research Laboratories,
Langley Court, Beckenham,
*Kent BR3 3BS, UK and *London*
Foot Hospital, Fitzroy Square,
London, UK
Correspondence to:
Dr D. T. Langford

Onychocryptosis, frequently termed 'ingrown nail' has been attributed to a multiplicity of factors including faulty nail-trimming[1-6], abnormally shaped nail plates or nail folds[6,7], excessive sweating[5], tight footwear[1,5], poor hygiene[3], excessive weight-bearing[6], inherited factors and trauma[3,8]. It is more common in males, having a 2:1 sex ratio and affecting patients most commonly between 10 and 30 years of age. It is frequently a recurring disease and numerous conservative and surgical treatments have been advocated.

Many factors cited as relevant to the development of the disease are based on opinion although three large series of patients have been studied by Fowler[5], Vandenbos and Bowers[6] and Lloyd-Davis and Brill[2]. None included comparative control subjects. The remaining literature is anecdotal and the variations in the normal population of the risk factors purported to be relevant to the development of the condition have not been defined. It is clearly essential to collect comparative data on potential risk factors in both patients and unaffected controls if there is to be any attribution of risk.

The following study was designed, therefore, to compare a number of parameters that might be relevant as risk factors in patients and age and sex-matched controls. It was conducted in two stages.

Materials and methods

Study 1

Fifty patients attending the London Foot Hospital were entered into the study. Patients were included providing that no surgical intervention had occurred and that only one foot was affected (unilateral disease). This enabled the unaffected foot to be used for comparison with control subjects in relation to anatomical parameters.

An age and sex-matched control group was obtained from employees of the Wellcome Research Laboratory (Beckenham, Kent, UK) and from pupils of the Cardinal Vaughan School (West Kensington, London, UK).

Patients and controls were assessed by questionnaire and by examination for a variety of parameters derived both from the literature and from observations by the authors (*Table 1*).

Sweat gland counts were obtained from the soles of the feet after occlusion in polythene for 5 minutes using the colloidal graphite technique described by Thomson and Sutarman[9]. This technique allows identification of both active and inactive glands.

Nail thickness was measured with Vernier callipers at the mid-point of the free edge of the nail. Medial rotation of the great toe was assessed

Table 1 *Variables used in statistical comparisons*

1. Family history of the disease	—scored present or absent
2. Body weight	
3. Shoe size	
4. Weight:shoe-size ratio	
5. Bunching of the toes	—scored present or absent
6. Mode of cutting	—convex short —convex —straight short —short
7. Sweat glands (total)	
8. Sweat glands (percentage active)	
9. Sedentary occupation	—scored present or absent
10. Nail fold width	
11. Nail thickness	
12. Divergence of nail folds	—scored present or absent
13. Medial rotation of great toe	—scored present or absent
14. Picking of the toes	—scored present or absent
15. Nail up to end of nail fold	—scored present or absent
16. Subjective opinion of sweating	—more than average —average —less than average
17. Foot hygiene	—average —less than average
18. Cross-sectional area of toe	
19. Curvature ratio of nail	
20. Lateral angle of nail	
21. Medial angle of nail	

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in the standing position because it tends to occur during weight-bearing. Both feet were assessed in patients and controls.

The nail fold width, the parallelism of the folds (i.e. divergence or convergence) and the cross-sectional area of the toes was assessed from a plaster replica of the toe which was obtained using dental impression material and dental plaster. The nail curvature was determined using anterior photographs of the casts. Three parameters were identified to assess the relevance of the variable curve of the nail: lateral and medial angle and a nail curvature ratio. These are represented in *Figure 1*.

Both toes were examined in all subjects and comparisons were made between the mean values for the controls and the values obtained from the unaffected toes of the patients. The measurements used for the controls were based on the mean values from both feet as there was no significant difference between left and right feet; the mean, therefore, provided the most precise measure available.

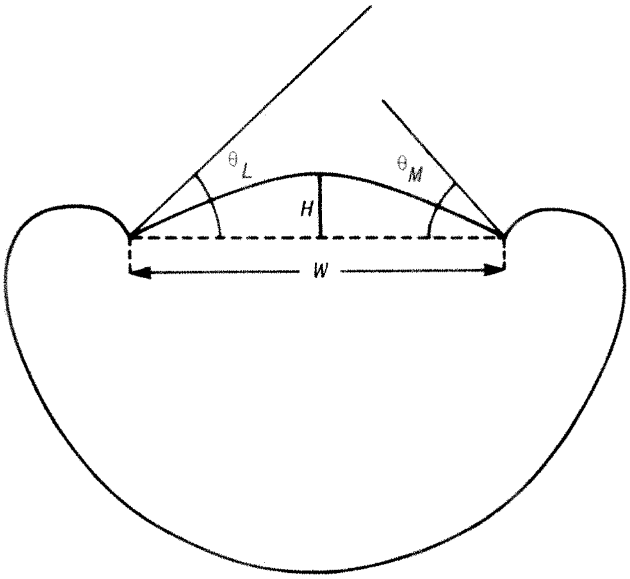

Figure 1 *Diagrammatic anterior cross-sectional view of a right toe cast showing the measurements used for nail curvature. Curvature ratio, H/W; θ_L, lateral angle; θ_M, medial angle*

Use of measurements from a single foot for patients but from the mean of both feet for controls may result in some difference in variability between the groups. It was felt that the discriminant analysis would be robust to these differences because intrapatient variability is small compared with interpatient variability.

Interdependencies of the 21 variables were tested within each group using *t* tests, χ^2 tests or Spearman's correlation as appropriate. The data were then analysed by linear discriminant analysis using stepwise multiple regression in order to identify a subset of the variables which would discriminate well between the controls and patients.

Study 2

Following the identification of such a subset of variables and the subsequent derivation of a potentially predictive equation for ingrown nail, a further patient sample was assessed for these subset variables. A total of 62 further patients attending the London Foot Hospital were examined for nail fold width, nail thickness and the presence or absence of medial rotation by a number of independent observers using Vernier callipers and assessment of rotation in the standing position; 35 controls were similarly examined. The resultant data were substituted in the equation in an attempt to substantiate the potential of such measurements as predictors of the disease.

Results

Study 1

The comparability of the patient and control groups for age and sex is shown in *Figure 2*. Features of the patient sample are shown in *Table 2* and are comparable to other patient surveys in terms of male predominance and lateral nail fold involvement.

Significant differences were found in patients between affected and unaffected toes for parameters such as nail fold width and mean cross-sectional area due to inflammatory oedema and infection. The presence of disease in one great toe did not induce medial rotation of the great toe of the other foot by causing excessive weight-bearing on the unaffected side. Medial rotation was consistently either present or absent in both great toes of all patients. No significant differences in anatomical parameters were found between right and left toes in controls, including medial rotation of the great toes. Mean values for anatomical measurements in controls were thus compared with measurements from the unaffected toes of patients.

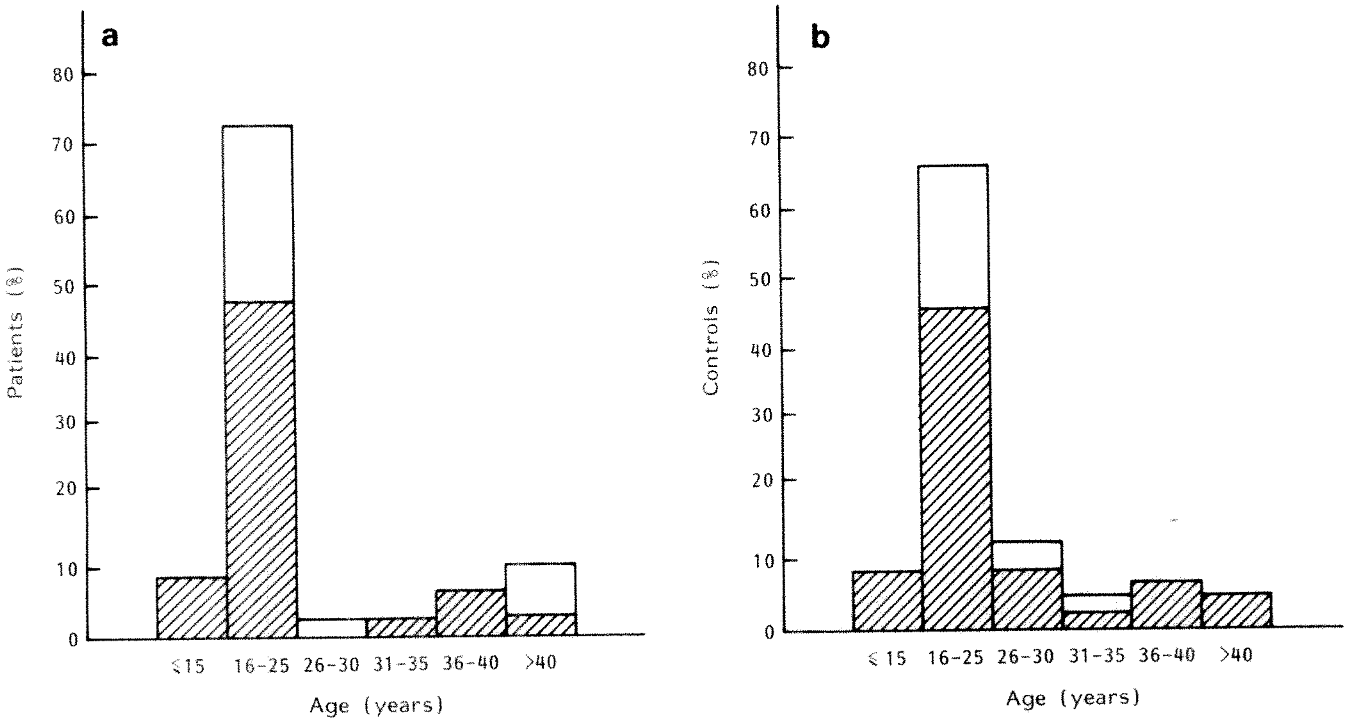

Figure 2 *Age and sex distribution of patients and control subjects. Patients: mean age 23·9 years, range 11–69 years;* □, *females* (n = *17*); ▨, *males* (n = *33*). *Controls: mean age 24 years, range 11–64 years;* □, *females* (n = *15*); ▨, *males* (n = *35*)

Twenty-one variables were available for analysis (*Table 1*).

In a comparison for each variable between the groups the only observed differences related to toe and nail anatomy and a family history of the disease. Patients tended to possess wider nail folds and thinner, flatter nails than control subjects and also more commonly volunteered a family history of the disease in first- and second-degree relatives. It was interesting that many of the factors previously proposed in the literature as being relevant to the development of ingrown nail were found to be equally common in patients and controls.

The interdependence of the variables was tested within each group using χ^2 tests, t tests or correlation depending on the types of variables. Nail curvature, nail thickness and nail fold width were found to be interdependent to varying degrees.

In order to construct the simplest possible predictive model, the data were analysed by linear discriminant analysis using stepwise multiple regression in order to identify a subset of variables which together would discriminate well between the controls and patients.

The following factors were found to be significant: (1) nail fold width (approximate P value $<0{\cdot}001$); (2) medial rotation (approximate P value 0·015); (3) nail thickness (approximate P value 0·030). The remaining variables did not approach significance once these first three had been entered.

The linear discriminant function (z) was calculated as:

$$z = x_1 - 5{\cdot}13x_2 + 67{\cdot}8x_3$$

where x_1 = nail fold width in inches × 10^{-3}
x^2 = nail thickness in inches × 10^{-3}
x_3 = 1 if medial rotation was present,
0 if medial rotation was absent
(5·13 and 67·8 are the regression coefficients)

The z value half-way between the two group means was 253 so this value was used to discriminate between potential sufferers and non-sufferers: thus if z was <253, subjects were classed as potential non-sufferers, but if z was >253, subjects were classed as potential sufferers. Using this criterion it was possible to attempt reclassification of patients and controls: the criterion classified 77 per cent of controls and 86 per cent of patients correctly.

Table 2 *Features of patient sample*

Parameters	Percentage of patients ($n=50$)
Male sex	66
Involvement of the right toe	50
Involvement of the medial fold only	14
Involvement of the lateral fold only	72
Involvement of both folds	14
Presence of pus	72
History of direct trauma	32
Presence of previous episodes	30

Table 3 *Age and sex of subject (study 2)*

	Patients	Controls
No. of subjects	62	35
Mean age (range) in years	21·9 (9–55)	21·8 (10–63)
Sex ratio (M:F)	1·9:1	1:1·5

Study 2

The age and sex of the patients and controls in the second phase of the study are shown in *Table 3*. There was an imbalance of sex ratio between the two groups studied but the age balance was comparable. In view of the male predominance of the condition this might be expected to enhance slightly the separation of z values between patients and controls, although the incidence of the condition in previously unaffected individuals is probably <1 in 50.

The calculation of linear discriminant function (z values) for patients and controls is shown in *Figure 3*. It should be noted that 65 per cent of patients achieved z values in excess of any z values seen in control subjects.

It can be seen that using the cut-off point of 253 it is possible to classify correctly 28 of the 35 controls (80 per cent) and 53 of the 62 patients (85 per cent). This is a better predictive result that that seen in Study 1 but is of a similar order.

Discussion

Previous studies on onychocryptosis have concentrated on the affected toe. It is evident from this study that distortions in the anatomy occur owing to the disease process and that measurements taken from such toes would reflect those distortions. Significant differences were detected between the right and left toes of patients for cross-sectional area and nail fold width. Therefore, only patients with unilateral disease were included in the study, thereby allowing measurements to be made from the unaffected toe. This obviated the source of error created by distortions due to the disease process. This was clearly important in the design of the study because it was anticipated that anatomy would be significant in determining risk of developing the disease. The finding of significantly thinner nails, thicker nail folds and a greater prevalence of medial rotation in the normal toes of patients compared with controls confirmed the importance of this aspect of study design.

The patients studied were found to be similar to those studied by other authors such as Lloyd-Davis and Brill[2] with regard to age, male predominance and involvement of the lateral nail fold. The majority of patients were in the 16–25-year age group and male patients outnumbered female patients by 2:1, confirming that this is primarily a disease of young men. The involvement of the lateral fold in 72 per cent of patients is similar to the frequency of 84 per cent described by Fowler[5] and suggests a mechanical or anatomical predisposition. Such predispositions were reinforced by a history of previous episodes of ingrown nail in 30 per cent of the patients.

In view of the large number of parameters meriting investigation it was necessary to control this study by studying an age and sex-matched group of healthy patients who had never

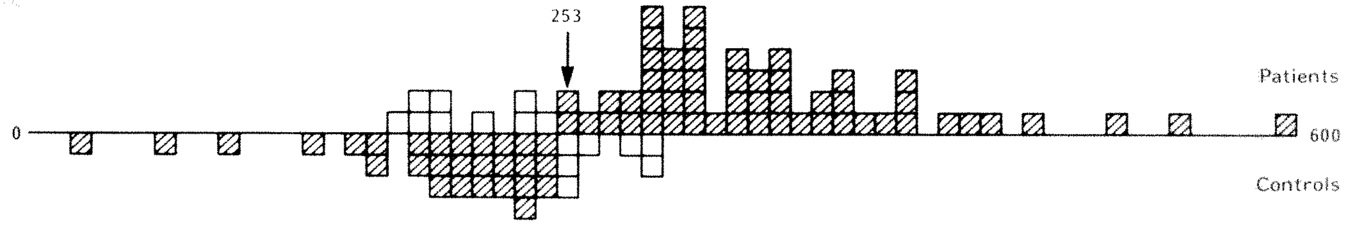

Figure 3 *Distribution of linear discriminant function (z) values, Study 2. The discriminating variables are nail fold width, nail thickness and medial rotation of the big toe. Controls: 28 (▨) with a z value <253, (80 per cent), seven (□) with a z value >253; patients: 53 (▨) with a z value >253 (85 per cent), nine (□) with a z value <253*

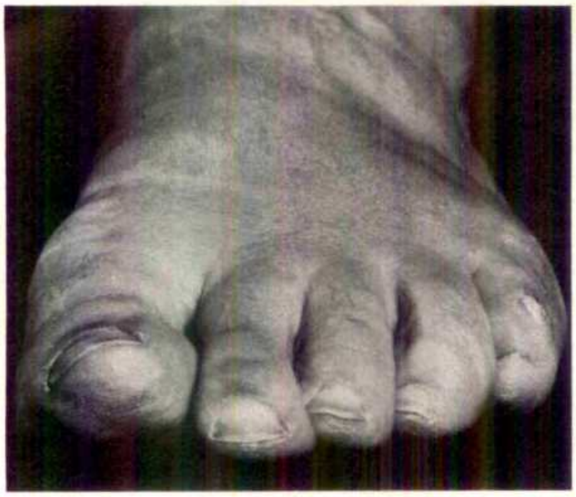

Figure 4 *Anterior view of left foot (adult female) showing medial rotation of the great toe occurring during weight bearing*

suffered with onychocryptosis. The possibility that the control group may contain subjects who would subsequently develop ingrown nail was considered. The incidence of the disease is difficult to ascertain but Clarke and Dillinger[1] found an incidence of 2·9 per cent in infantrymen. As these were all men and a recognized high-risk group it is unlikely that more than 1 in 50 of the controls would subsequently suffer from the disease. Consideration was also given to whether the presence of a diseased toe on one foot might place excessive load on the unaffected foot and distort the toe anatomy or influence medial rotation. Medial rotation was not affected by this, being consistently either present or absent in both great toes of patients. The effect of weight bearing on nail fold width is unlikely to be significant. The great toes take little weight when standing and the additional load which occurs during limping is transferred largely to the heel. Limping is uncommon in patients with ingrown nail; most patients experience pain only if footwear is rubbing or if the toe suffers direct trauma.

A family history of the condition in first- and second-degree relatives was twice as common in patients as in controls, suggesting a familial nail or toe shape. This was reinforced by the statistically significant differences in nail fold width and nail thickness between the unaffected toes of patients and those of controls. Patients tended to have wide, fleshy nail folds and thin nail plates.

The incorporation of correlation between variables and the use of stepwise multiple regression analysis identified three key variables that were significantly different between the two groups: nail fold width, medial rotation of the great toe, and nail thickness. These results were clearly indicative of an anatomical predisposition combined with the presence of medial rotation in patients. Such an anatomical situation would explain the occurrence of the condition during weight bearing when the thin nail plate could erode the nail fold, particularly if a sharp edge were produced by faulty nail cutting. It would also explain why the disease is so frequently recurrent and intractable and why total nail avulsion without nail bed destruction frequently leads to a recurrence of the ingrown nail because this procedure does not remove either underlying risk factors. The disappearance of the disease with increasing age would be expected for a variety of reasons such as effective treatment or increased thickness of the toe nail with age.

The anatomical predisposition would also explain the effectiveness of surgical treatments such as wedge resection of the nail folds, practised by Vandenbos and Bowers[6], and removal of a longitudinal strip of nail adjacent to the affected fold followed by localized cautery of the nail bed at the base of the nail strip. The latter procedure, described by Murray and Robb[10], is less traumatic than either a wedge resection of the folds[6] or a wedge resection involving both a strip of nail and some of the nail fold, as described by Palmer and Stevenson[11]. All three procedures reduce the nail/nail-fold contact in such patients and therefore medial rotatory motion would not roll the nail fold across the nail plate during walking.

Medial rotation of the great toe is present while weight bearing and absent while the foot is off the ground. It therefore means that there is repetitive medial rotation and derotation with every footstep in walking. This movement would cause the nail to move in relation to the lateral nail fold which would be inhibited from movement by contact with the adjacent toe. This would explain the high preponderance of lateral fold involvement and why a thinner nail plate that has been cut correctly or incorrectly may penetrate the nail fold. *Figure 4* illustrates the effect of medial rotation on the lateral nail fold.

The use of linear discriminant function analysis to provide the best separation between patients and controls, using nail fold width, nail thickness and medial rotation as discriminating variables, allowed the derivation of an equation with a high level of predictive ability. This equation provides a numerical value by substitution of three simple measurements. The nail thickness at the central point of the free edge of the nail and the nail fold width can be measured by use of Vernier callipers and the presence of medial rotation can be assessed during weight bearing.

In order to consider the possibility of using the equation as a predictor in high-risk groups such as police cadets or infantry, it was necessary to validate the model in a further group of patients and controls. The second phase of the study was conducted by independent observers and resulted in a very similar distribution of linear discriminant function values for patients and controls, classifying 80 per cent of controls and 85 per cent of patients correctly.

This study provides a rationale for less traumatic surgical approaches to ingrown nail than nail avulsion with or without nail bed ablation. Removal of a nail strip with ablation of the related nail bed is frequently adequate. It may also be valuable to be able to identify subjects at high risk of this disabling condition so that they could be educated to avoid trigger factors such as excessive walking.

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Variceal haemorrhage after failed injection sclerotherapy: the role of emergency oesophageal transection

S. A. Jenkins and R. Shields

University Department of Surgery, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP, UK

Correspondence to:
Mr S. A. Jenkins

In a planned sequential policy for the emergency control of continued bleeding from oesophageal varices, oesophageal transection was performed after failure of conservative treatment, including injection sclerotherapy. In 15 patients who underwent emergency oesophageal transection, bleeding was controlled by operation in the majority (87 per cent), but 11 of the 15 patients died in hospital. Mortality in patients with poor liver function (Child's C) was 100 per cent, the majority of deaths resulting from hepatic and renal failure. The results of this study suggest that emergency oesophageal transection to control acute variceal haemorrhage is associated with a poor prognosis in patients with poor liver function and questions its role in a sequential emergency treatment policy.

Keywords: Variceal haemorrhage, injection sclerotherapy, emergency oesophageal transection

In recent years it has become increasingly clear that injection sclerotherapy, either alone or in combination with vasoactive drugs and balloon tamponade, is effective in controlling acute variceal haemorrhage in approximately 95 per cent of patients[1–5]. However, when sclerotherapy fails to control bleeding or prevent its early recurrence, it is essential to identify other forms of treatment which can be employed in sequence. Surgical intervention, which is now rarely used as an initial treatment for bleeding varices, is usually called upon when sclerotherapy fails. Because portal systemic shunting carries high operative mortality and morbidity rates when undertaken as an emergency, especially in patients with poor liver function[6,7], most surgeons would choose oesophageal transection to control the bleeding. In these circumstances, operation is performed after the patient has been bleeding for some time and the results of operative intervention at this stage in treatment may not be as good as when initiated earlier. We report our experience with oesophageal transection, in a planned management policy, for patients in whom bleeding could not be controlled by resuscitation, conservative treatment and injection sclerotherapy.

Patients and methods

Between January 1980 and December 1986, 127 patients presented with their first variceal haemorrhage (index bleed) and were treated primarily by injection sclerotherapy. This treatment was administered either on admission, in which case it was usually the sole treatment, or within a few hours when on many occasions preliminary control was attempted with vasopressin or balloon tamponade. In all but eight of these patients (94 per cent) bleeding was controlled. In addition, 54 patients who experienced recurrent variceal haemorrhage on a maintenance sclerotherapy programme were admitted to hospital; in 47 (87 per cent) control was achieved. In eight patients with an index bleed and seven patients with recurrent variceal bleeds (interval bleeders), haemorrhage could not be controlled by conservative treatment. Oesophageal transection was carried out using an EEA stapling gun (Auto Suture Company, UK) inserted into the oesophagus via a small gastrostomy[8,9]. The clinical data of the 15 patients who underwent oesophageal transection are shown in *Table 1*.

Operation

The technique was essentially that described by Johnston[10]. Usually the abdomen was opened through a midline epigastric incision and intra-abdominal vascular adhesions divided between ligatures. The left lobe of liver was mobilized by incising the left triangular ligament and the abdominal oesophagus was mobilized by incising the overlying peritoneum. Vagal trunks were identified and tapes passed around each. Large paraoesophageal varices around the lower 10 cm of the oesophagus were individually ligated and divided to provide extrinsic devascularization. The left gastric vascular axis was identified and ligated in continuity by two separate linen threads. Where feasible, veins around the upper part of the stomach were ligated, along with the short gastric veins, to extend the extrinsic devascularization. A stout linen thread was passed round the abdominal oesophagus, within (i.e., to exclude) the taped vagal trunks. Through a small gastrostomy in the upper third of the anterior wall of the stomach an EEA stapler (No. 27) was inserted into the stomach, and the head passed into the oesophagus to ensure that the ligature, when tightened onto the shaft of the stapler, would be at, or just above, the cardio-oesophageal junction. After the ligature was tied, the head of the stapler was closed and fired. After the removal of the stapler the gastrostomy was closed in two layers.

Results

The in-hospital mortality rate of oesophageal transection used in this particular therapeutic sequence was 11 out of 15 patients (73 per cent) (*Table 2*). Bleeding recurred in two patients (13 per cent) and therefore postoperative recurrent haemorrhage did not constitute a problem.

Table 1 *Preoperative clinical data of patients undergoing oesophageal transection*

Men	8
Women	7
Age (years)*	51.5 ± 12.0 (30–72)
Child's grading	
A	2
B	4
C	9
Ascites	11
Hepatic encephalopathy	6
Aetiology of portal hypertension	
Extrahepatic block	2
Cirrhosis	
Alcoholic	7
Chronic active hepatitis	4
Cryptogenic	2

* The mean ± s.e.m. values are given with the range in parentheses

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Table 2 *Complications and outcome of the 15 patients undergoing oesophageal transection*

Patient	Child's classification	Complications	Outcome
1	A	None	Survived
2	A	None	Survived
3	B	None	Survived
4	B	None	Survived
5	C	Continued bleeding, cardiac arrest	Died day 1
6	C	Liver failure	Died day 1
7	B	Adult respiratory distress syndrome	Died day 11
8	C	Liver failure	Died day 8
9	C	Liver failure	Died day 16
10	C	Liver and renal failure	Died day 8
11	C	Liver and renal failure	Died day 2
12	B	Cardiac and respiratory arrest	Died day 29
13	C	Liver and renal failure	Died day 14
14	C	Continued bleeding, progressive liver failure	Died day 32
15	C	Liver and renal failure	Died day 6

The transfusion requirements of the four patients who survived the operation (12·5 ± 7·32 units, range 4–20) was less than that of those who died postoperatively (22·2 ± 10·9 units, range 6–41), but the difference did not achieve statistical significance ($P = 0{\cdot}13$).

The majority of deaths following oesophageal transection resulted from progressive hepatic and renal failure. Survival was closely related to liver function at the time of operation as assessed by Child's grading. Neither of the two patients in Child's group A died, of the four patients with Child's B grading, two (50 per cent) died while in hospital. All of the nine patients in Child's C grade died in hospital (100 per cent). Of the 11 patients who died following oesophageal transection, gross ascites was present in nine and hepatic encephalopathy in six. Of the patients who survived the operation none displayed evidence of hepatic encephalopathy before the operation, but two had mild ascites. The hospital mortality rate of the Child's C patients whose bleeding was controlled by conservative tratment and who did not require oesophageal transection was 44 per cent (21/48) for the first-time bleeders and 46 per cent (13/28) for interval bleeders.

Laboratory data other than those included in the Child's grading were not especially helpful in predicting outcome (*Table 3*). Of the haematological parameters the only significant difference between the groups was in the platelet count, survivors having significantly higher counts than those who died. The concentrations of total bilirubin, urea and creatinine were lower, and albumin levels were significantly higher, in the four patients who survived the operation than in the 11 patients who died. There were no significant differences in the plasma levels of liver enzymes, total protein, globulin or direct bilirubin between the two groups of patients.

Of the four patients who survived oesophageal transection two have not experienced further variceal haemorrhage (5 years in one patient, 9 months in one patient) and in both no further varices have been observed at follow-up gastroscopy. The two remaining survivors have both experienced recurrent variceal haemorrhage. The first of these patients presented with an acute variceal bleed 7 months after oesophageal transection and was successfully treated initially with injection sclerotherapy. However, the patient continued to have severe recurrent variceal bleeding, and approximately 9 months after transection underwent an elective portacaval shunt from which she made an uneventful recovery. The second patient experienced a massive upper gastrointestinal haemorrhage approximately 3 years after oesophageal transection and died at another hospital before he could be resuscitated.

Discussion

For the control of acute variceal haemorrhage, injection sclerotherapy has pride of place and operation is usually restricted to those in whom injection sclerotherapy and other measures, e.g. somatostatin, have failed. The results of this study show that surgery, placed later in a sequential treatment policy, is associated with a high death rate, related more to poor liver function than to complications of operation or recurrence of bleeding.

Until recently procedures involving a direct attack on the varices were relatively unsuccessful particularly in western countries, because of a high rate of recurrent bleeding or of leakage at the oesophagogastrointestinal anastomosis. However, oesophageal transection using an EEA stapling device is a technically simpler operation and, since it does not seem to affect liver blood flow, should not theoretically impair liver function or precipitate hepatic encephalopathy. Moreover, further surgical procedures such as portasystemic shunt are not precluded. Consequently, transabdominal oesophageal transection is widely advocated for the treatment of oesophageal varices.

Emergency portasystemic shunting is highly successful in controlling bleeding, but the price is prohibitively high mortality[6,7]. Moreover between 20 and 30 per cent of patients who survive the operation can be expected to develop hepatic encephalopathy[11,12]. There are, therefore, few surgeons who would advocate shunting as an initial treatment for variceal haemorrhage.

The timing of oesophageal transection remains debatable. Our own experience and that of Johnston[10] show that oesophageal transection carries a much lower mortality under elective circumstances than in an emergency. However this difference in outcome, related to the timing of treatment, is found with any therapy for bleeding oesophageal varices. There are those who advocate oesophageal transection much earlier in the therapeutic sequence. The results of several trials comparing oesophageal transection to injection sclerotherapy as the primary initial treatment are awaited with interest. However, despite its simplicity, oesophageal transection remains a more formidable procedure than injection sclerotherapy and is therefore unlikely to have a place as initial treatment when the patient is admitted to hospital with the first haemorrhage. Most clinicians have recourse to oesophageal transection when initial conservative measures have failed, but the outcome in these circumstances, at least in our experience, is bleak.

Variceal haemorrhage which does not respond to conservative measures is frequently associated with a poor prognosis for several reasons—irreversible shock, aspiration pneumonia, hepatic failure and complications of treatment. Oesophageal transection was successful in controlling bleeding in most of the

Table 3 *Laboratory data of patients surviving or dying after emergency oesophageal transection*

	Patients surviving operation ($n = 4$)	Patients dying after operation ($n = 11$)
Platelets ($\times 10^9$/l)	107 ± 23	58·6 ± 10*
Prothrombin ratios	1·55 ± 0·23	1·67 ± 0·13
KCCT ratio	1·14 ± 0·05	1·2 ± 0·06
Haemoglobin (g/dl)	9·6 ± 0·68	10·42 ± 0·21
Total protein (g/dl)	58·7 ± 2·8	54·8 ± 2·42
Albumin (g/dl)	32·5 ± 1·6	27·7 ± 2·16*
Globulin (g/dl)	26·3 ± 2·3	26·9 ± 1·82
Alkaline phosphatase (units/l)	147 ± 56·6	195·4 ± 43·9
Total bilirubin (μmol/l)	20·75 ± 6·51	122 ± 28·8*
Direct bilirubin (μmol/l)	5·5 ± 2·27	60·6 ± 19·2
Alanine aminotransferase (units/l)	23·25 ± 4·07	47·1 ± 14·3
γ-GT (units/l)	88·25 ± 58·94	170·2 ± 51·29
Urea (mmol/l)	2·98 ± 0·15	13·64 ± 2·65*
Creatinine (mmol/l)	48·15 ± 14·5	91·2 ± 9·65*

Results are expressed as mean ± s.e.m., * denotes a significant difference between the groups ($P < 0{\cdot}05$). KCCT, kaolin and cephalin clotting time; γ-GT, γ-glutamyl transferase patients but the hospital mortality rate was 73 per cent. In this series death was associated mainly with hepatic impairment. In most of these patients there was clear evidence before operation of dysfunction of the liver and impaired hepatic reserve as measured by the Child's classification. There may also be a degree of renal impairment since the plasma creatinine levels of the patients who died after transection were significantly higher than those of the survivors. These findings are consistent with other reports on the use of emergency oesophageal transection in the treatment of uncontrollable variceal bleeding, where the prognosis for the patient with poor hepatic function is extremely poor[13–18]. Consequently we believe that the effectiveness of emergency oesophageal transection in the patient whose bleeding cannot be controlled by conservative means is limited and that good results can be anticipated only in those patients with good, or slightly impaired, liver function (Child's A and B grades).

The problem remains about what to do with high risk patients who continue to bleed after injection sclerotherapy. Certainly, since blood loss and transfusion are poorly tolerated by the cirrhotic patient, surgical treatment should be instituted as early as possible to prevent the deterioration that is inevitably associated with prolonged conservative management. Even so, although the evidence is somewhat limited, the results of randomized controlled clinical trials published to date suggest that early oesophageal transection does not greatly improve the survival of patients with poor liver function[19–21] Alternatively more powerful vasoactive agents, e.g. somatostatin[22], or more vigorous injection sclerotherapy may control bleeding, even temporarily, in those high risk patients, allowing for a more definitive procedure to be undertaken electively when the patient is more suitable for operation. The latter suggestion is supported to some extent by the present study in which the mortality rate of Child's C patients whose bleeding was controlled by conservative means. including injection sclerotherapy was 44 per cent in first-time bleeders which, although high, is considerably better than the 100 per cent mortality rate in those who continued to bleed who underwent oesophageal transection Therefore there is circumstantial evidence that even in those with severe liver impairment (Child's C) the prognosis is better when bleeding is brought rapidly under control.

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Timing of prophylactic antibiotics in abdominal surgery: trial of a pre-operative versus an intra-operative first dose

T. Bates, G. Siller,
B. C. Crathern,
S. P. Bradley,
R. D. Zlotnik,
C. Couch,
R. D. G. James and
C. M. Kaye

The William Harvey Hospital,
Kennington Road, Willesborough,
Ashford, Kent TN24 0LZ, UK

Correspondence to.
Mr T. Bates

When prophylactic antibiotics are used in abdominal surgery it is customary to give the first dose before the operation. Whilst intra-operative antibiotics may be effective in elective surgery, there may be an advantage to starting pre-operatively when there is already an infective focus such as appendicitis. Antibiotics started pre-operatively (group P) have been compared with antibiotics started after initial abdominal exploration (group T). Three intravenous doses of 500 mg metronidazole plus 1 g cephazolin were given in a randomized, double-blind study of 700 emergency and elective high-risk abdominal operations. Antibiotic plasma concentrations at the end of the operation were significantly lower in group P but lay well within the therapeutic range. Wound infection rates, which included minor and delayed infections, were similar in both groups (group P, 57 of 342, 16·7 per cent; group T, 55 of 358, 15·4 per cent; 95 per cent confidence intervals for the difference being −4·1 to +6·7 per cent. In appendicitis, wound infection rates were 12·1 and 13·9 per cent for groups P and T respectively. However, non-fatal deep sepsis was more common in group P (nine cases) than in group T (two cases) ($\chi^2 = 4·9$, $P < 0·05$). Postoperative infection was twice as common in obese patients whose body mass index (BMI) was ≥ 26 (39 of 132, 30 per cent) than in thin patients whose BMI was <24 (41 of 288, 14 per cent; $\chi^2 = 13·8$, $P < 0·001$). This study failed to show any advantage to starting antibiotics pre-operatively, even in appendicitis.

Keywords: Metronidazole, cephazolin, prophylaxis, laparotomy, wound infection, intra-abdominal sepsis, lengths of stay, obesity

When prophylactic antibiotics are used in abdominal surgery it is widely accepted that the first dose should be given pre-operatively[1,2] and this view stems from the experimental work of Burke[3]. Stone and his colleagues[4] have confirmed that postoperative antibiotics are ineffective and, in a critical review of the literature on prophylactic systemic antibiotics, Chodak and Plaut considered any study in which therapy was not begun pre-operatively to be inadequate[5].

The giving of an antibiotic is sometimes overlooked in the preparation for emergency surgery until an unexpected focus of sepsis or soiling is found at operation. There is considerable evidence that antibiotics are effective when given intra-operatively[6] and even when they are placed in the wound at the end of the procedure[7,8].

Pre-operative intravenous cephaloridine has been compared with a similar dose placed in the wound at the end of laparotomy and although no overall difference was found there did appear to be an advantage to the earlier treatment in appendicitis[9]. Brumfitt and Hamilton-Miller[10] have made a plea for further studies into the timing and duration of prophylactic antibiotics and the present study was undertaken to determine the optimum time of administration of the first dose.

It was decided to use three doses of antibiotics since the effectiveness of this regimen is established[11–14] and to use the agents cephazolin[4,15,16] and metronidazole[17–21] which are well tried in abdominal surgery to cover both aerobic and anaerobic organisms[22,23].

Wound infection rates have been compared in a randomized double-blind trial of antibiotics started pre-operatively and antibiotics started after initial abdominal exploration in patients undergoing emergency or at-risk abdominal operations.

Patients and methods

Eligibility

All patients aged ≥ 16 years in one of the two surgical firms of a district general hospital having emergency abdominal operations, repair of strangulated hernias or elective colorectal operations were included. Elective cholecystectomy was included if one or more of the following criteria were present· age >65 years, jaundice, rigors within 1 week, previous biliary surgery, planned exploration of the common bile duct[24]. Elective gastroduodenal operations were included if one or more of the following criteria were present carcinoma of the oesophagus or stomach, gastric ulcer, pyloric stenosis, bleeding ulcer, current treatment with ranitidine or cimetidine[1]

Exclusions (before randomization)

Patients were excluded if they were known to be allergic to penicillin or either of the agents used, if the operating surgeon considered that pre-operative antibiotics were essential, or if the patient had received antibiotics within the previous week

Trial design

Trial packs contained three doses of each of two antimicrobial agents. They were consecutively numbered and arranged from a table of random numbers to contain placebo drugs for either the pre-operative dose or for the intra-operative dose (*Table 1*)

The antibiotics

Each patient received three active doses of 500 mg metronidazole intravenously over 20 min plus 1 g cephazolin as an intravenous bolus,

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the first dose being either pre-operative (group P) or intra-operative (group T). The pre-operative dose was given at the same time as the routine premedication. The placebo doses were prepared to resemble the respective active drug so that the clinical investigators were unaware of the composition of any pack.

Losses

All eligible patients who were not entered into the trial (i.e. were not randomized) were recorded and the completeness of records was cross-checked against the operating theatre record book.

Withdrawals (after randomization)

Those patients who were ineligible on the protocol were withdrawn (e.g. if antibiotics had been given within 1 week pre-operatively or if the patient had a cholecystectomy without a stated risk factor). If the operation was cancelled or if the delay after the pre-operative dose was greater than 12 h, patients were also withdrawn from the study.

Missing data

The following patients were not withdrawn after randomization. Dose violations were recorded if protocol antibiotics were omitted or delayed. Some patients had additional antibiotics either in continuity with the trial doses or after an interval. The operative findings did not always necessitate opening a viscus, e.g. in disseminated malignancy, but these patients were not withdrawn. Patients with missing data were included in the study.

Concentrations of antimicrobials in plasma

In 21 patients plasma concentrations of metronidazole and cephazolin were measured on induction of anaesthesia, and then at hourly intervals for 3 h. The concentrations of metronidazole and cephazolin in each plasma sample were determined simultaneously by high performance liquid chromatography. To each plasma sample (100 μl) was added methanol (200 μl) containing the internal standard, 9048 RP (the 2-ethyl analogue of metronidazole). After mixing, the samples were allowed to stand in the dark at room temperature for 4 days. After mixing and centrifuging, aliquots of the supernatant were injected into the chromatograph. The analytical column (internal diameter 15 cm × 4·6 mm) contained Hypersil ODS (Shandon Southern Products, Ltd., Runcorn, UK) (3 μm), and the mobile phase consisted of 0·01 M aqueous potassium dihydrogen phosphate (pH 3·0), methanol and acetonitrile in the proportion of 93·12:3 volume/volume, respectively, at a flow rate of 1·1 ml/min. The compounds of interest were detected in the column eluate by their ultraviolet light absorbance at 300 nm. The retention times were about 4·5 min for metronidazole and about 7·0 min for cephazolin. The coefficients of variation of the method for each drug were <10 per cent at 1 and 10 μg/ml for metronidazole, and 5 and 50 μg/ml for cephazolin, with limits of detection of about 0·5 μg/ml for metronidazole and 2 μg/ml for cephazolin.

Follow-up

All patients who did not have a wound infection whilst in hospital were seen about 1 month after operation. They were asked if there had been any discharge from the wound after they left hospital and if this information was missing from the outpatient notes they were subsequently contacted by telephone or letter.

Risk factors

The following variables were considered: age, sex, body mass index (BMI = weight in kg/(height in metres)^2), diagnostic category (*Table 2*), degree of peritonitis (*Table 3*), grade of surgeon, interval from pre-operative dose to operation, duration of operation, dose violations, and severe sepsis found at operation considered to require continuation of antibiotics after the protocol doses (continuous antibiotics).

Table 1 *Trial design*

Dose no.	Time	Group T (intra-operative)	Group P (pre-operative)
1	Premedication	Placebo	Antibiotics
2	Intra-operative	Antibiotics	Placebo
3	6 h after premedication	Antibiotics	Antibiotics
4	12 h after premedication	Antibiotics	Antibiotics

Table 3 *The severity of peritoneal inflammation in the intra-operative and pre-operative groups*

	Group T (intra-operative)	Group P (pre-operative)
Appendicectomy		
Normal	33 (27%)	24 (22%)
Acute appendicitis, histology +ve	54	52
Gangrenous	6	6
Perforated	29	25
Total	122	107
All other operations		
No inflammation	186	182*
Inflamed organ	23	13
Gangrenous organ	4	10*
Localized infection or abscess	15	15*
Generalized purulent peritonitis	7	13*
Faecal peritonitis	1*	2*
Total	236	235
Total number of patients (deaths within 24 h)	358 (1)	342 (5)

* Includes one patient who died within 24 h of operation

Table 2 *Diagnostic category and wound infection in the intra-operative and pre-operative groups*

	Group T (intra-operative)		Group P (pre-operative)	
	Infected	Total	Infected	Total
Colorectal resection	25	116 (21·6%)	24	101 (23·8%)
Appendix	17	122 (13·9%)	13	107 (12·1%)
Strangulated hernia	0	12	1	15
Cholecystectomy + duct exploration	1	8	1	14
Cholecystectomy alone	0	13	2	16
Oesophageal or gastric operation	4	22	6	27
Insertion Celestin tube	0	6	1	4
Perforated ulcer oversown	0	4	1	8
Closure colostomy	1	9	0	4
Small bowel obstruction/resection	3	21	4	19
Cancer of pancreas	0	8	1	10
No viscus incised	1	8	2	10
Other	3	9	1	7
Total	55	358 (15·4%)	57	342 (16·7%)

Table 4 *A comparison of the results of the study in the two groups*

	Group T (intra-operative)	Group P (pre-operative)
Total number of patients	358	342
Wound infection		
Major	34 (9·5%)	32 (9·4%)
Minor	10	15
Delayed	11	10
Total	55 (15·4%)	57 (16·7%)
Deep sepsis (non-fatal)	2	9
Mortality (30 day)		
Septic	6 (1*)	6 (2*)
Sepsis-related	3	9 (2*)
Non-septic	3	9 (1*)
Total	12 (1*) (3·4%)	24 (5*) (7·0%)
Postoperative days of fever		
Mean* (days)	2·06	2·10
>10 days (patients)	4	12
Length of postoperative stay		
Mean* (days)	9·55	9·69
15–29 days (patients)	41	47
30+ days (patients)	13	14
Patients receiving interval antibiotics (for urinary infection)	34 (50%)	45 (60%)

* Deaths within 24 h, excluded for means

Outcome events

The outcome was assessed as follows Wound sepsis was categorized as major, minor or late (criteria of Pollock and Evans[25]) and deep sepsis was recorded separately The causes of death within 30 days were categorized as septic, sepsis-related (e.g. mesenteric infarction) or not septic (e g terminal malignancy, even if at home) The number of postoperative days in which fever was noted to be >37·5°C was recorded Postoperative infection requiring antibiotics (interval antibiotics) was considered an outcome event. Length of postoperative hospital stay included the day of discharge but not the day of operation Formal outcome evaluation of each patient was completed and agreed between at least two authors before the double-blind code was broken.

Consent

The trial protocol was approved by the district ethical committee and all patients signed consent to the investigation after verbal and written explanation

Estimation of required sample size

In order to make an estimate of the number of patients required in each arm of the study to avoid a type II error (the conclusion that there is no difference between two groups when a real one exists), the following assumptions were made. The proportion of events was estimated to be 20 per cent and a clinically important reduction would be from one-third to 13 per cent Using Feinstein's formula[26,27] with α 0·05 and β 0·20, it was calculated that 437 patients would be needed in each arm of the trial

Statistical methods

Data were analysed on an RM Nimbus PC2 (Research Machines, Oxford, UK) microcomputer using SL microstatistical software (Questionnaire Service Company, East Lansing, USA). This enabled comparison of risk factors and outcome events The χ^2 test was used to compare wound infection and deep sepsis rates in the two groups and the extremes of BMI Approximate 95 per cent confidence intervals were calculated for the difference between the groups in respect of wound infection. Drug concentrations in the two groups were compared using the Mann–Whitney *U* test because the data were highly skewed

Results

There were 750 eligible patients available for the study between Februrary 1982 and March 1986. Over the same period, 75 otherwise eligible patients were excluded: 58 patients had had antibiotics within 1 week; in 12 patients pre-operative antibiotics were considered essential; 3 patients were allergic to penicillin; and 2 patients refused consent. There were 33 losses of eligible patients, for 9 of whom there were no trial drugs available and the remainder were forgotten. There were 17 withdrawals after randomization, 8 of which were unavoidable due to a cancelled or postponed operation and the remainder were entered but ineligible There were therefore 700 evaluable patients, being 93 per cent of those eligible and 98 per cent of those entered into the trial.

Wound infection

The overall wound infection rates were similar in both groups, being 16·7 per cent in group P and 15·4 per cent in group T (*Tables 2* and *4*). The 95 per cent confidence intervals for the difference are from −4·1 to +6·7 per cent. Nineteen per cent of wound infections occurred at home, mostly after appendicectomy. Major wound infection, which often delayed discharge from hospital, occurred in just under 10 per cent of patients in both groups.

Comparison of risk factors and outcome

The two groups were well matched for diagnostic categories (*Table 2*) and severity of appendicitis (*Table 3*). There were, however, twice as many patients with generalized or faecal peritonitis in group P. Furthermore, there were four patients with fatal mesenteric infarction in group P and none in group T. The mean age in the 2 groups was similar (*Table 5*) but there were 12 more patients aged ≥80 years in group P. This was a serious imbalance since 18 of the 35 deaths were in patients of this age.

There were twice as many deaths in group P, five of which occurred within the first 24 h compared with one in group T. Of those surviving more than 1 day, eleven deaths in group P were sepsis-related and eight in group T There was a higher incidence of non-fatal deep sepsis in group P (nine cases) compared with group T (two cases; $\chi^2 = 4{\cdot}9$, $P < 0{\cdot}05$).

Of the 11 patients with deep sepsis, 5 had a BMI ≥26. Rather more patients in group T had a BMI ≥26 (*Table 5*). Of 132 patients with a BMI ≥26, 39 had a sepsis-related outcome (30 per cent) compared with 14 per cent of the 288 with a BMI <24 ($\chi^2 = 13{\cdot}8$, $P < 0{\cdot}001$; *Table 6*).

There were more patients in group T with a delay between the pre-operative dose and the start of operation but in this group the first dose was placebo. No correlation was found

Table 5 *Risk factors compared between the intra- and pre-operative groups*

	Group T (intra-operative)	Group P (pre-operative)
Total number of patients	358	342
Age ≥80 years	32 (9%)	44 (13%)
Age (mean ± s.d.)	53 ± 22 years	55 ± 22 years
Men	172	169
BMI (mean ± s.d.)	23 ± 4	23 ± 4
BMI <24	140 (39%)	148 (43%)
BMI ≥26	73 (20%)	59 (17%)
Sepsis at operation (not appendicitis)	27 (11%)	40 (17%)
Registrar operation	155	156
Interval first dose to operation >3 h	25	10
Duration of operation >3 h	47	48
Dose violation (omitted or delayed)	14	11
Continuous antibiotics	10	10

Missing data excluded in percentage calculation (16 for T, 26 for P); BMI, body mass index

Table 6 *Body mass index compared with sepsis-related outcome*

BMI*		Sepsis-related outcome†	
Value	No. patients	No. patients	%
≥26	132	39	30‡
≥24 but <26	238	45	19
<24	288	41	14‡
Unknown	42	—	—

* BMI, body mass index (weight/height^2); † sepsis-related outcome = wound infection, deep sepsis, septic death or sepsis-related death; ‡ χ^2 test comparing highest and lowest infection rates ($\chi^2 = 13·8$, $P < 0·001$)

between the pre-operative interval and any of the outcomes examined.

There were more patients in group P with persistent fever, prolonged postoperative stay and receiving therapeutic antibiotics (*Table 4*). The overall mean duration of postoperative fever and length of stay was, however, similar in both groups.

There was no obvious association between grade of surgeon and outcome. Patients whose postoperative course was complicated by hospital wound infection, deep sepsis, septic death and sepsis-related death were more likely to have had a longer operation than those whose course led to non-septic death or who had delayed or no wound infection. Patients with deep sepsis or hospital wound infection stayed much longer in hospital and had more days of fever than other patients Therapeutic antibiotics were used in three of the nine septic deaths, one of the sepsis-related deaths and four other patients with wound infection. There was no obvious association between dose violation and outcome.

Microbiological isolates

Details of the micro-organisms isolated are available on application to the authors.

Follow-up

Seventeen patients (2·4 per cent) were lost to follow-up with regard to delayed wound infection, nine of whom died from malignancy within 4 months.

Missing data

The most common missing data were measurements of patients' height so that BMI was not calculated for 16 patients in group T (4·5 per cent) and 26 in group P (7·6 per cent).

Fate of withdrawals

There were eleven withdrawals in group T and six in group P, of whom three in each group did not have an operation. One patient in group T, who was withdrawn because the operation was delayed for 36 h after the first dose, died from an anastomotic dehiscence following left hemicolectomy. One patient in group P who was withdrawn because she had had pre-operative antibiotics was found to have an inoperable carcinoma of the ovary and had a minor postoperative wound infection. She left hospital but died within 30 days. There was no other complication amongst the withdrawals.

Concentrations of antimicrobials in plasma (Figure 1)

Concentrations of metronidazole were significantly higher in group T than in group P at 1, 2 and 3 h after induction of anaesthesia whilst cephazolin levels were higher at 1 and 2 h ($P < 0·05$, Mann–Whitney U test). However, concentrations of the two antibiotics remained well within the therapeutic range (4 times the mean inhibitory capacity) for the expected organisms in both groups throughout the 3-h period. Concentrations of metronidazole declined only slightly in 3 h, whereas those of cephazolin more than halved

Discussion

This study failed to show any advantage to starting prophylactic antibiotics pre-operatively in abdominal surgery, even in appendicitis[9] where this could be regarded as treatment rather than prophylaxis[28].

It is difficult to explain why the patients receiving pre-operative antibiotics (group P) appeared to have a higher incidence of non-fatal deep sepsis. It is possible that the lower plasma levels of cephazolin at the completion of operation may have been important, but these concentrations lay well within the therapeutic range in the few cases tested. Furthermore, there was no relationship between the length of the interval from the pre-operative dose to the intra-operative dose and the outcome. There is no suggestion from this study that giving antibiotics with the premedication is of any advantage and it seems likely that a high plasma and tissue concentration at the time of operation is the most important factor.

The slow decline in the plasma concentrations of metronidazole compared with those of cephazolin is consistent with the long plasma elimination half-life of metronidazole of around 8 h[29], whereas that for cephazolin is much shorter, in the range 1–3 h[30]. The trial design meant that in group T the second and third antibiotic doses were sometimes given only 4 h apart, which for metronidazole was unnecessary. The intervals, however, were chosen in order to avoid giving a large number of placebo doses. When these drugs were given pre-operatively a better estimate of elimination half-life could be made than in group T patients, where drug distribution as well as elimination would be occurring in part of the 3-h period under study. The values obtained for their plasma elimination half-life are similar to those reported in the literature for healthy ambulant individuals. It can therefore be tentatively concluded that a major operation and the underlying disease have virtually no effect on the elimination of either of these drugs.

Obesity has been shown to be a risk factor for wound infection in abdominal surgery[31,32] but a consideration of this

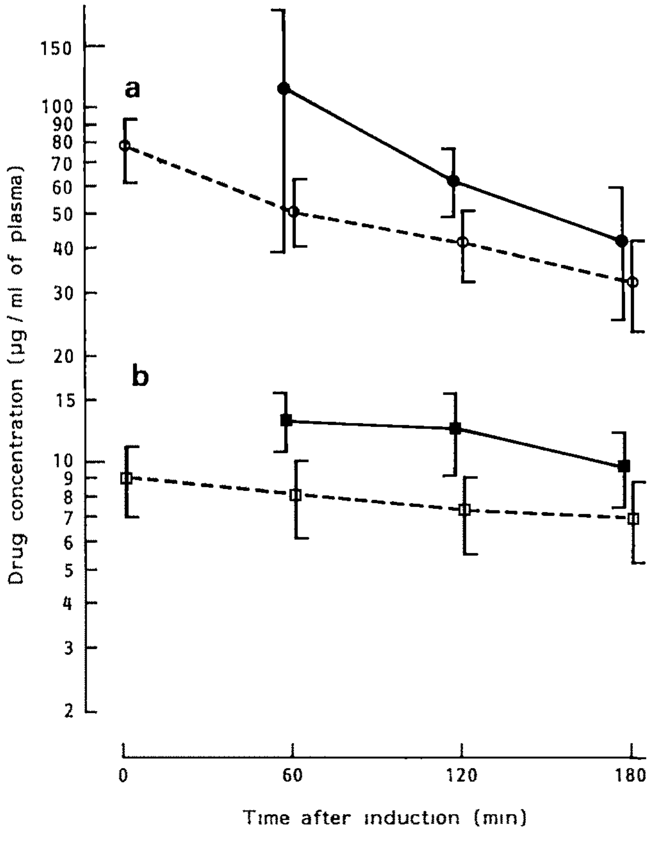

Figure 1 *Mean (±s.d.) plasma levels (µg/ml) of* **a** *cephazolin and* **b** *metronidazole in patients given intravenous cephazolin (1 g) and metronidazole (500 mg) pre-operatively (– – –) or intra-operatively (——). Pre-operative group P, n = 11, intra-operative group T, n = 10*

factor is often omitted from clinical trials comparing wound infection rates. BMI (Quetelet's index)[33] was found to be a sensitive discriminator.

The wound infection rates in this study are much higher than have been reported by Matheson's group[34,35] and, although a few others[36] have managed to achieve such low rates, it seems likely that greater attention to the prevention of intra-operative soiling and possibly the addition of antibiotic peritoneal lavage may be beneficial. It is difficult to be certain that we have not come to rely too heavily on powerful systemic antibiotics and are less meticulous with peritoneal toilet and wound protection.

The number of evaluable patients in this study fell short of the estimated sample size by 20 per cent but wound infection rates were so close in the two groups that if there is a real advantage to giving antibiotics pre-operatively it seems most unlikely that it would ever be demonstrated by increasing the size of the study Whilst it is possible that these results carry a type II error in that real differences in outcome may have been missed in relatively small subgroups, it is unlikely that there is a clinically important advantage to giving antibiotics with the premedication rather than during the course of operation for patients requiring abdominal surgery.

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Posterior sagittal anorectoplasty for reoperation in children with anorectal malformations

A. J. L. Brain and E. M. Kiely

*Hospital For Sick Children,
Great Ormond Street,
London WC1N 1EH, UK*

Correspondence to:
Mr A J. L. Brain

A prospective study was carried out in 12 consecutive patients (7 boys and 5 girls), to evaluate posterior sagittal anorectoplasty for patients incontinent of faeces after anorectal reconstruction. Examination revealed anatomical problems such as: recurrent fistula (two), massive urethral diverticulum (one), absent vagina (one), and a missed urogenital sinus (one). Preliminary electromyography showed the external sphincter to be displaced from the anus in nine patients. Posterior sagittal anorectoplasty, with correction of anatomical defects and precise reconstruction of bowel within the sphincters, was carried out after the formation of a loop colostomy. No postoperative complications were observed. Contrast studies confirmed healed suture lines before stoma closure. Follow-up, between 4 and 46 months, revealed good faecal control in only two patients, with a significant improvement in two others. The rest remained incontinent although sensation was improved. These disappointing results, at variance with other published reports, lead us to conclude that posterior sagittal anorectoplasty, when used as a secondary procedure, is good for correcting anatomical defects but not for improving faecal continence.

Keywords: Posterior sagittal anorectoplasty, anorectal anomalies, faecal incontinence

Incontinence of faeces following surgery for supralevator anorectal anomalies remains a problem. More than one-third of patients may have a poor result[1]. This may be due to misplacement of bowel in relation to the muscles of continence, or to pathology such as a recurrent fistula. Reoperation may be difficult with a disappointing outcome. However, several authors have reported good results using a posterior sagittal approach as a salvage procedure for failed primary surgery[2–4]. This approach gives excellent exposure and has led to a clearer understanding of the surgical anatomy. Pena[4] has even claimed that posterior sagittal anorectoplasty (PSARP) as a secondary operation is easier than when the same operation is carried out as a primary procedure. For these reasons we set up a prospective study to evaluate PSARP for the salvage of patients incontinent of faeces after anorectal reconstruction.

Patients and methods

A consecutive series of twelve children (five girls and seven boys), whose faecal incontinence after previous surgery for anorectal anomalies made them socially unacceptable, were included in the study Their ages ranged from 5 to 17 years (median 11 years). All seven boys and one of the girls had been born with a supralevator anorectal anomaly with a fistula Primary surgery, as listed in *Table 1*, had been carried out in the first year of life. Two girls who were born with a cloaca had had a primary abdominoperineal pull through. The other two girls had been diagnosed as having a vestibular ectopic anus. One had a neonatal cutback and the other an anal transposition at the age of 6 years.

Before presentation and inclusion in this study, eight of the twelve children had already had one or more unsuccessful attempts at secondary surgery This included various types of anoplasty, proctoplasty and levatorplasty. One boy had a 'redo' pull through (*Table 1*)

Table 1 *Patients, defects and previous surgery*

Patient	Sex	Age (years)	Anomaly	Primary procedure*	Salvage procedures
1	M	8	High ARA	Abdominoperineal pull through	None
2.	F	7	Vestibular ectopic anus	Transposition	Repair rectovaginal fistula
3	M	13	High ARA	Abdominosacral anal pull through	Levatorplasty Secondary levatorplasty
4.	F	14	Cloaca	Abdomino-anal pull through	None
5.	M	17	High ARA	Anorectal pull through	Proctoplasty
6.	F	16	High ARA	Abdominoperineal pull through (at age 12 years)	Anal reconstruction with skin
7.	F	7	Vestibular ectopic anus	Anal cut back	Hendren anoplasty
8	M	15	High ARA	Abdominosacroperineal pull through	Anoplasty Levatorplasty
9.	M	10	High ARA	Sacro-abdomino-anal pull through	'Redo' pull through
10.	M	14	High ARA	Pull through	Levatorplasty
11.	M	10	High ARA	Abdominoperineal pull through	None
12.	F	5	Cloaca	Abdominoperineal pull through	None

ARA, Anorectal anomaly; * primary procedure as described by the surgeon who carried out the operation

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At presentation all patients were completely incontinent of faeces with minimal sensation and no control.

Assessment included thorough clinical examination, under anaesthesia if necessary, as well as needle electromyography of the pelvic floor and anal sphincters In nine children electromyography showed the anal sphincter to be displaced from the anus Neuropathic changes were identified in two. Examination showed the pelvis and/or perineum to be extensively fibrosed with anorectal stenosis in six patients. A massive urethral diverticulum, representing the fistula remnant, was found in one boy with recurrent urinary tract infections. One girl was found to have an absent vagina In another the urethra was found to enter a urogenital sinus. A recurrent recto-urethral and a rectovaginal fistula were found in two other children. Two of the twelve patients in the series were found to have a sacrum with only three segments

A loop colostomy was formed either before or at the time of the PSARP. A thorough mechanical preparation of the bowel was carried out with washouts, and clear fluids by mouth for 48 h before operation. A single dose of broad spectrum antibiotics (ampicillin, gentamicin and metronidazole) was given on induction of anaesthesia. The operation was carried out in the manner described by Pena and deVries[5,6] through a posterior sagittal approach, with tapering of the bowel and relocation within the reconstructed sphincters. After the operation a contrast study was carried out via the distal limb of the stoma to confirm healing. The anus was calibrated with Hegar's dilators to ensure an adequate calibre, between 12 and 16, depending on the size of the child. In ten children the stoma was subsequently closed between 3 and 7 months postoperatively. In one patient the stoma was closed after only 3 weeks because of social pressure as he lived abroad and would be unable to return for further surgery In another child, stoma closure was postponed until 14 months after PSARP, because of impending school examinations

Results

No early postoperative complications were observed. Suture lines healed without infection and without clinical or radiological evidence of a leak. Colostomy closure was carried out in all 12 children without morbidity. They have been followed up for between 4 and 46 months (median 30 months). In only four children have there been any improvements in faecal control. Two of these are now completely continent. They have good sensation with only occasional staining and no frank incontinence. The other two are much improved with good sensation but imperfect control. An improvement in sensation was observed in four of the eight others However all eight children still have socially unacceptable incontinence of faeces (*Table 2*).

The posterior sagittal approach was found to give excellent exposure allowing correction of the anatomical defects. No recurrence of the anorectal stenoses, the massive urethral diverticulum, the recto-urethral or the rectovaginal fistulae has been observed. The absent vagina was successfully reconstructed One patient was found to have mild anal stenosis with circumferential prolapse, 6 months after operation. The stenosis was not severe, was easily dilated and has not recurred 3 months later. In the girl with a urogenital sinus, some breakdown was noted between the newly constructed urethra and vagina On follow-up, 13 months after surgery, she was found to have greatly improved urinary continence.

Discussion

We found that only two of the twelve patients became socially continent of faeces following PSARP. Two others were much improved These results are disappointing when compared with other published reports.

The literature on the posterior sagittal approach for failed primary surgery is scanty. However published reports to date show encouraging results. As early as 1971 Stephens and Smith[2], 'using an operative approach similar if not identical to that termed posterior sagittal'[3], reported a good functional improvement in continence in seven out of ten patients. deVries[3] reported good results using PSARP for reoperation in two children, both of whom became socially continent. Similarly in a series of eight patients, reported by Pena[4], five had an immediate 'excellent' result with continence of faeces and no soiling. The other three were much improved but did still have occasional involuntary bowel actions.

Our disappointing results may be due to either the operation in our hands, or to the patients in our series. The actual operative technique was very similar to that demonstrated by Pena (personal communication). The postoperative management was different. Pena recommends a strict regimen of dilatation[6,7] We did not routinely carry this out. Pena lists the factors that may influence the final result of PSARP as a salvage procedure[4]. These are: the original anatomy (height of the malformation and sacral anomalies); magnitude of damage at previous procedures; and age, intelligence, education and family environment. It is of note that the damage at previous procedures in our series was extensive. At least six of our patients had very severe fibrosis, reflecting the severity of the complications following the previous surgery. This may be the reason for our poor results when compared with other series. Surprisingly, one of the two patients with a good result was also found to have severe fibrosis at operation. Of our two patients with a short sacrum, one had a good result, contrary to Pena's findings. We have incomplete data on the height of the original fistulae in our patients There is no reason to suspect that they were different from those in other series. Two of the girls in our series had primary surgery for low anorectal anomalies. The results of PSARP for salvage in these patients were as bad as in those with a high anomaly. The patients in our series were of a similar age to those in other series. There is no reason to suspect that their intelligence, education, or family environment were any different either.

Table 2 *Findings, salvage procedure and results*

Patient	Findings	Salvage procedure	Follow-up (months)	Faecal continence
1.	Urethral diverticulum, sphincter behind anus	Excision of diverticulum, PSARP	30	Incontinent
2	Rectovaginal fistula, dense fibrosis, sphincter behind anus	Fistula closed, PSARP	22	Incontinent
3.	Sphincter behind anus	PSARP	34	Incontinent
4	Urogenital sinus, sphincter behind anus	Vaginoplasty, urethroplasty, PSARP	25	Improvement
5	Short sacrum, sphincter behind anus	PSARP	33	Incontinent
6	Frozen pelvis, complete anal stenosis	PSARP with abdominal mobilization of colon	4	Improvement
7.	Wound breakdown, absent vagina, sphincter behind anus	Vaginoplasty, PSARP	20	Incontinent
8.	Severe fibrosis, sphincter behind anus	PSARP	30	Incontinent
9	Dense fibrosis, two rectal strictures, recto-urethral fistula	Strictures resected or divided, fistula closed, PSARP	31	Excellent
10	Sphincter behind anus	PSARP	23	Incontinent
11.	Fibrosis, sphincter behind anus, short sacrum	PSARP	39	Excellent
12.	'Frozen pelvic floor'	Urethroplasty, vaginoplasty, PSARP	46	Incontinent

PSARP, posterior sagittal anorectoplasty

We found the pulled through bowel to lie anterior to the external sphincter complex on pre-operative electromyography in nine of the twelve patients. This finding was confirmed at operation; deVries and Pena report similar findings[3,4].

One patient in our series developed mild anal stenosis. We did not regularly dilate the anus after operation. Pena recommends that this should be done for a minimum of 3 months[6].

Pena and deVries[6] have emphasized the suitability of the posterior sagittal approach for the repair of rectovaginal fistulae and cloacal anomalies. This may be combined with an abdominal mobilization of rectum or vagina when insufficient length is obtained from below In only one of our patients did we have to mobilize the rectum from above. We confirmed Pena and deVries' finding that the posterior sagittal approach allows excellent exposure. It enables more precise identification of the anatomy and hence reconstruction. Heavy retraction is unnecessary. This may have been a significant contributory factor to the lack of postoperative sepsis.

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Announcement

Reviews

The Editorial Board of *The British Journal of Surgery* continues to invite review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium of £100. Potential authors seeking advice on the suitability of review topics are advised to contact: Professor D. C Carter, Regius Professor of Clinical Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors invite submissions of signed leading articles to *The British Journal of Surgery*. These articles should be 600–1000 words in length, should address controversial topics of current interest and should be supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium of £100 is payable on publication. Potential authors seeking advice on the suitability of topics are advised to contact: Professor D. C. Carter, Regius Professor of Clinical Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Surgical workshops

The Editors invite the submission of articles describing technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they can be accompanied by no more than two figures but should not carry supporting references. Articles submitted to the Surgical Workshop series may be subjected to external review and assessment by the Editorial Board before acceptance.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is likely to be high. Authors are advised to restrict such reports to a maximum of 500 words, to use no more than five references and to submit no more than one illustration.

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Paget's disease of the anus: a clinicopathological study

N. C. Armitage,
J. R. Jass,
P. I. Richman*,
J. P. S. Thomson and
R. K. S. Phillips

*St. Mark's Hospital, City Road, London, and *St Bartholomew's Hospital, West Smithfield, London, UK*

Correspondence to
Mr N. C. Armitage, Department of Surgery, University Hospital,
Nottingham NG7 2UH, UK

Paget's disease of the anus is a rare disorder of controversial origin and is frequently associated with malignancy. We studied eight patients and carried out immunohistochemical studies to determine whether particular functional profiles might be indicators of a malignant association. One patient presented with synchronous carcinoma and two developed carcinomas 3 and 10 years after excision of Paget's disease. Five patients underwent wide local excision and have not developed cancer (median follow-up 6 years, range 5–13 years). However, four patients developed recurrent Paget's disease. Immunohistochemical studies showed that in general Paget cells stained positively with CAM 5.2 (a cytokeratin marker), gross cystic disease fluid protein (a marker for apocrine cells), human milk fat globule glycoprotein (HMFG 1 and 2) and carcinoembryonic antigen but negatively for PR3A5 (a marker for colonic goblet cells). Three cases had a staining profile which was quite different from that usually observed and these were associated with malignancy. One showed an antigenic profile more typical of a large bowel carcinoma. Paget's disease of the anus appears to run one of two clinical courses: to develop malignancy; or to recur locally, often on repeated occasions. Wide local excision is the treatment of choice but long-term follow-up is necessary because of the cancer risk. An immunohistochemical staining pattern which is different from usual may indicate a higher malignant risk and/or identify some cases of Paget's disease as representing a downward 'pagetoid' extension from a anorectal adenocarcinoma rather than a true epidermotropic apocrine neoplasm of the perianal skin.

Keywords: Extramammary Paget's disease, immunohistochemistry

Paget's disease of the anus is a rare perianal disorder of unknown aetiology. The first report was by Darier and Couhllaud in 1893[1], 19 years after Sir James Paget first described the characteristic breast lesion[2]. It has been postulated that extramammary Paget's disease is: a sweat gland carcinoma[3]; an intraepidermal metastasis of adenocarcinoma usually of sweat gland origin[4], a multicentric local process[5]; or a special type of squamous carcinoma[6]. The list of putative cell types of origin for Paget cells is equally varied: primitive multipotential epidermal cells[7], melanocytes[8], keratinocytes[9] and cells of both eccrine and apocrine sweat glands[10,11]. Recent work has supported the view that Paget cells in extramammary Paget's disease are of glandular origin, as they contain low molecular weight cytokeratins and carcinoembryonic antigen (CEA)[12–14]. Furthermore their apocrine nature is indicated by the expression of gross cystic disease fluid protein (GCDFP) antigen[15,16].

Paget's disease of the anus is reported as being associated with a fairly high risk of malignant change either at presentation or at a later date. In a recent literature review, Beck and Fazio[17] showed an overall risk of associated malignancy of 73 per cent. In their own ten patients, three had invasive cancer at the time of presentation and a further two developed cancer during follow-up. Five other patients remained disease-free after wide local excision, although the follow-up period was a median of only 2 years (0·4–4·2 years). Williams *et al.*[18] reported associated cancer in five of their seven patients. The remaining two patients underwent multiple wide excisions for recurrent disease over the following 12 and 17 years respectively, emphasizing the need for long follow-up.

Paget's disease of the anus raises questions with regard to: the cell type of origin, whether the disease represents a low-grade malignancy or is a sign of synchronous cancer, and whether there is a method that can identify individuals who are at risk of developing malignancy. We have undertaken a study of patients who have been treated for Paget's disease of the anus at St. Mark's Hospital with the aim of identifying clinical and immunohistochemical differences which might distinguish between those who develop malignant change and those who remain free from invasive cancer. In particular, we have considered the possibility that Paget's disease may represent two quite distinct entities: (i) an epidermotropic neoplasm arising from perianal apocrine glands; and (ii) downward 'pagetoid' spread by signet ring cells stemming from an anorectal adenocarcinoma.

Patients and methods

A review was made of the case notes of eight patients treated at St Mark's Hospital with a histological diagnosis of perianal Paget's disease at the time of treatment. They included four patients previously reported in 1977 by Lock *et al.*[19], one of whom has also been reported separately[20,21]. Particular attention was paid to the incidence or subsequent development of malignancy and recurrence of Paget's disease in those patients who did not develop malignant disease.

Histological sections of the eight cases of Paget's disease were prepared and stained with haematoxylin and eosin for pathological review. Six cases of signet ring cell carcinoma of the rectum were included in the study, one of which was associated with downward pagetoid spread involving the perianal skin. Serial sections were stained for the presence of mucins by means of Alcian blue at pH 2·5, PAS-diastase and PB/KOH/PAS[22]. Additional levels were cut and processed by an immunoperoxidase technique using monoclonal antibodies recognizing a low molecular weight cytokeratin (CAM 5.2)[23], other glandular epitopes, human milk fat globule glycoprotein (HMFG) 1 and 2[24] and CEA (C46)[25] (kindly donated by Amersham International plc,

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Table 1 *Details of three patients with Paget's disease of the anus with associated malignancy*

Patient	Age (years)	Sex	Symptoms	Treatment	Histology	Follow-up interval (years)	Status
A	85	F	4 months: lump	(a) Biopsy/colostomy	Paget's and mucinous adenocarcinoma		
				(b) Fast neutron radiotherapy			
				(c) Closure of colostomy			Died at 9 years
B	76	M	9 months of soreness	(a) Biopsy	Paget's	3	
				(b) Biopsy of pelvic mass	Mucinous adenocarcinoma		Died at 2 months
C	55	F	12 months of soreness	(a) Wide local excision	Paget's	2	
				(b) Wide local excision	Paget's	6	
				(c) Wide local excision + split skin graft + stoma	Paget's	2	
				(d) Inguinal block dissection	Poorly differentiated adenocarcinoma		Died at 3 years

Table 2 *Details of five patients with Paget's disease of the anus without associated malignancy*

Patient	Age (years)	Sex	Symptoms	Treatment	Histology	Follow-up interval (years)	Status
D	73	F	12 months of soreness	(a) Wide local excision + split skin graft	Paget's	2	
				(b) Wide local excision	Paget's	1	
				(c) Wide local excision	Paget's	1	
				(d) Vulvectomy	Paget's	⩽1	
				(e) Wide local excision	Paget's	1	
				(f) Wide local excision	Paget's	2	Alive with recurrent disease
E	75	F	48 months of soreness	(a) Biopsy	Paget's		
				(b) Radiotherapy + 5-fluorouracil cream		4	
				(c) Wide local excision + split skin graft	Paget's	2	
				(d) Biopsy	Paget's		
				(e) Wide local excision	Paget's	2	Well
F	63	F	Anal lump	(a) Biopsy	Paget's	⩽1	
				(b) Excision scar	Paget's	5	Well
G	64	M	5 months of soreness	(a) Wide local excision	Paget's	5	
				(b) Biopsy + creams	Paget's	2	
				(c) Wide local excision + split skin graft		2	
				(d) Colostomy			Died
H	77	F	—	(a) Biopsy	Paget's	1	
				(b) Biopsy	Paget's	⩽1	Alive with recurrence

UK), a mucinous epitope expressed by colorectal goblet cells (PR3A5)[26] and an apocrine marker, GCDFP (BRST.2, CRL Cambridge Research Laboratories, UK)[15,16] An indirect immunoperoxidase technique with the avidin–biotin detection system (Amersham International plc) was employed. Antibodies were undiluted except for CEA (1.5) and GCDFP (1:40). Antibodies were from authors in references where no commercial source is given All sections were reviewed by a single pathologist (J.R J.) who was unaware of the clinical details and scored for the presence or absence of the particular marker.

Results

Patients

There were six women and two men with a median age of 75 years (55–85 years). The median follow-up period was 6 years (0·5–13 years). Six presented with perianal soreness and two with a lump. Symptoms had commonly been present for some time with a median of 6 months (4–48 months). The eight patients fell into two groups: those with malignancy either at the time of presentation or on follow-up (three patients) and those who remained free from invasive cancer (five patients).

Details of the three patients with associated malignancy are shown in *Table 1*. Only one patient (A) had malignancy at presentation. She was treated with fast neutron radiotherapy and survived a further 8 years; she died from carcinomatosis at the age of 93 years. Two patients (B and C) developed tumours at 3 and 10 years respectively after their initial presentation. Patient B was treated by radiotherapy for a squamous carcinoma of the tongue 2 years before presenting with a pelvic mass from which he died 2 months later. Patient C died from widespread disease 3 years after a bilateral block dissection for inguinal nodes containing poorly differentiated carcinoma. The latter patient has been the subject of two previous case reports[20,21].

Five patients (*Table 2*) did not develop cancer but four of them developed recurrent Paget's disease. Four patients are

Table 3 *Results of immunohistochemical studies and mucin staining in patients with Paget's disease of the anus (A–H) or signet ring cell carcinoma of the rectum (I–N)*

Group	Case	Human milk fat globule glycoprotein 1 (HMFG 1)	Human milk fat globule glycoprotein 2 (HMFG 2)	Carcino-embryonic antigen (CEA)	Low molecular weight cytokeratin (CAM)	Gross cystic disease fluid protein (GCDFP)	PR3A5*	PB/KOH/PAS stain	Periodic acid–Schiff stain (PAS)
Paget's disease + carcinoma	A	–	–	–	–	–	++	+	++
	B	++	++	+	++	–	–	–	++
	C	–	+	++	++	–	–	–	–
Paget's disease	D	++	++	+	–	++	–	+	++
	E	++	+	–	++	+	–	–	–
	F	–	–	++	++	+	–	–	++
	G	++	+	++	++	+	–	+	++
	H	+	++	++	++	–	–	–	+
Signet ring cell carcinoma	I	+	++	++	++	+	–	+	++
	J	+	+	++	++	–	+	++	++
	K	+	+	++	++	–	–	+	+
	L	+	+	++	++	–	+	+	++
	M	–	–	++	–	–	+	++	–
	N	+	–	++	++	–	+	++	++

–, Negative/indefinite; +, focal or weakly positive, ++, diffuse and strongly positive, * marker for colonic goblet cells

under follow-up with Paget's disease of whom two have symptomatic recurrence and two are free from disease.

Histological studies

The amount of mucus varied between cases but was often less than that seen in signet ring carcinoma. The mucins were positive with PAS-diastase and Alcian blue (pH 2·5) but gave only a weak reaction or no reaction with PB/KOH/PAS. In contrast, three of six signet ring cell carcinomas were intensely positive with PB/KOH/PAS. The latter provided the only qualitative difference in the mucus histochemistry of Paget's disease and signet ring cell carcinoma

In six cases the Paget cells were strongly positive for cytokeratin, supporting their glandular origin. GCDFP was clearly positive in four cases and negative in four, three of the latter being cases A, B and C described in more detail below. CEA was present in most Paget cells but absent in cases A and E. Most Paget cells were positive for HMFG 1 and 2 but so were the majority of signet ring cell carcinomas though less intensely so With the exception of patient A, Paget cells were negative for PR3A5 whereas four signet ring cell carcinomas were positive In case A the PR3A5-positive cells resembled signet ring cells cytologically, and were negative for HMFG 1 and 2 and GCDFP. This patient had a synchronous anorectal mucinous carcinoma. In patient B, who developed a pelvic mucinous carcinoma 3 years after Paget's disease of the anus had been diagnosed, the Paget cells expressed a functional profile as that usually seen with Paget's disease, with the exception of GCDFP which could not be detected. In patient C the Paget cells had large pleomorphic nuclei and secreted no mucus. The poorly differentiated carcinoma which involved the inguinal lymph nodes showed similar cytology CEA and CAM 5.2 were the most strongly expressed antigens. GCDFP was not detected and HMFG 1 and 2 staining was indefinite and weak respectively. The details of the staining reactions are shown in *Table 3*.

Discussion

Paget's disease of the anus is rare At a specialist colorectal hospital there have been only eight documented cases since 1930. It has been said that the condition has a very high association with malignancy—as high as 86 per cent in some series[5]. In our study three of eight patients had associated malignancy, a figure lower than in previous reports, an apparent discrepancy which may have a number of explanations. Firstly, there may be a selection bias towards the association in the smaller series. Secondly, foci of carcinoma in Paget's disease may be small and overlooked, though our specimens were well sampled and examined with care. Finally, the pathological diagnosis is not easy. In particular Paget's disease needs to be distinguished from pagetoid spread by signet ring cells originating from an underlying anorectal adenocarcinoma. We believe that the latter phenomenon may have led to an inflated estimate of the risk of invasive malignancy. Our observations may help to clarify some of the difficulties posed by the pathological diagnosis.

We agree with the concept that Paget cells are of glandular and probably of apocrine origin. Five of our cases had what we would describe as a usual pattern of staining for Paget's disease, that is positive for cytokeratin[12,13], GCFDP[15,16], CEA[14] and HMFG 1 and 2[24] but negative for PR3A5[25]. These patients have not developed malignancy at a median follow-up period of 8 years. However they have a high recurrence rate which would support a hypothesis that Paget's disease is a low grade though often multicentric neoplastic change within the skin as suggested by Helwig and Graham[5].

Three cases had a staining pattern which differed from that described above and they were all associated with malignancy. In particular none expressed the apocrine marker GCDFP. In patient B, the mucinous adenocarcinoma of the pelvic region which developed did not show any particular histological resemblance to an apocrine tumour, and in case C the cytological atypia and marked differences in staining compared with typical Paget's disease might reflect an enhanced aggressiveness. On the other hand, patient A, where the staining pattern was completely different from the other cases (negative for all markers except PR3A5), almost certainly did not have Paget's disease at all but was an example of pagetoid spread from an anorectal mucinous adenocarcinoma. The Paget cells in this case were characterized by an abundance of intracytoplasmic nuclei and a small, hyperchromatic eccentric nucleus. Thus they resembled signet ring cells cytologically

Turning to the management of the condition, it seems that unless the patient is very frail the treatment of first choice is wide local excision with or without skin grafting. However four of our five patients who did not develop invasive malignancy did suffer from local recurrence, often on multiple occasions over a long time period. This is similar to the experience of Williams *et al.*[18] Beck and Fazio[17] have a much lower recurrence rate and they ascribe this to their policy of wide local excision with quadrant biopsy, and frozen section confirmation of clearance. However their follow-up period is short with a median of 2 years. Clearly a long follow-up is necessary both to assess recurrence and malignant potential. If, as in our experience, the disease is locally recurrent then it may be necessary to consider adjuvant therapy such as radiotherapy or topical/systemic chemotherapy. However, it must be remembered that some patients may live a long time with their disease requiring only symptomatic treatment.

In conclusion, this rare disease continues to pose problems in diagnosis and treatment. However the use of special staining may assist in the separation of genuine Paget's disease from pagetoid spread due to an anorectal adenocarcinoma. This would be an important distinction, with implications for patient management.

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Anorectal function after abdominal rectopexy: parameters of predictive value in identifying return of continence

K. Yoshioka, G. Hyland and M. R. B. Keighley

Department of Surgery, The General Hospital, Birmingham, UK

Correspondence to
Professor M R. B. Keighley, The Clinical Teaching Block, The General Hospital, Steelhouse Lane, Birmingham B4 6NH, UK

Posterior abdominal rectopexy was performed in 12 patients with a full-thickness rectal prolapse: 9 had faecal incontinence. The prolapse was successfully controlled in all cases and six of nine patients were rendered continent. Physiological studies in patients were compared with age- and sex-matched controls. Preoperative anal pressures were significantly lower than in controls at rest (R), during maximum pelvic floor contraction (Sq) and attempted defaecation (St) (R, $P<0\cdot005$*; Sq,* $P<0\cdot005$*; St,* $P<0\cdot005$*). Anorectal angles were significantly more obtuse in patients than in controls (R,* $P<0\cdot05$*; St,* $P<0\cdot025$*). None of these parameters changed significantly after abdominal rectopexy. Median rectal emptying significantly decreased after operation (preoperative 83 per cent/min; postoperative, 58 per cent/min,* $P<0\cdot05$*). Median perineal descent during attempted defaecation also significantly decreased after operation (preoperative, 8·5 cm; postoperative, 7·1 cm;* $P<0\cdot025$*). Parameters which predicted return of continence included: delayed leakage during the saline infusion test* ($P<0\cdot025$)*, a narrow anorectal angle during pelvic floor contraction* ($P<0\cdot025$)*, minimal pelvic floor descent during contraction* ($P<0\cdot05$)*, and a long anal canal at rest* ($P<0\cdot05$) *and during pelvic floor contraction* ($P<0\cdot025$).

Keywords: Abdominal rectopexy, anal canal pressure, perineal descent, pelvic floor descent, anorectal angle

Rectal prolapse is a distressing condition, not only because of the uncontrollable prolapse but because approximately two-thirds of these patients are also incontinent[1]. Many patients with rectal prolapse have exaggerated perineal descent[2] and the pudendal nerve may be damaged by prolonged straining[3].

Rectal prolapse can be successfully treated by posterior abdominal rectopexy[4–7] with a low rate of recurrence but faecal incontinence may persist in 30 per cent of patients despite an effective rectopexy[8]. We have undertaken paired physiological studies in 12 consecutive patients before and after Marlex® (C. R. Bard Incorporated, Massachusetts, USA) posterior abdominal rectopexy Results have been compared with age- and sex-matched controls to detect the functional abnormalities associated with a rectal prolapse. Paired studies have allowed us to identify those patients who are likely to remain incontinent after rectopexy and in whom an additional pelvic floor repair might be indicated.

Patients and methods

Twelve patients with a full-thickness rectal prolapse underwent posterior abdominal rectopexy as previously described[4] using polypropylene (Marlex) mesh between May 1982 and June 1987 All patients were women and had a median age of 57 years (range, 22–79 years) Clinical and physiological evaluation was carried out before and 3–6 months after operation Physiological studies were compared with 15 age- and sex-matched control patients (all women, median age 54 years (range, 32–73 years)) who had no gastrointestinal disease

Anal canal and sigmoid pressures were measured simultaneously at 2, 4 and 26 cm from the anal verge in the seated position on a specially designed chair. Manometry was performed using a water-perfused 4-channel catheter with side openings connected to a pressure transducer (Lectromed Ltd , UK) and multichannel recorder (MultiTrace 4, Lectromed, Ltd.). The catheter was introduced into the sigmoid colon with the patient in the left lateral position The position of the catheter was checked radiographically in five patients to establish the manometric characteristics of a blocked catheter. The catheter was fixed to the left buttock by tape Pressures were measured at rest, during maximum pelvic floor contraction and attempted defaecation. Rectal compliance and the rectoanal inhibitory reflex were assessed using a rectal balloon attached to the 4-channel catheter and positioned in the rectal ampulla just above the levator ani The balloon was also connected to a pressure transducer and pen recorder Intraballoon pressure responses to incremental 50 ml increases in intrarectal volume were measured over the range 0–400 ml of air Rectal compliance was calculated by dividing the increase in balloon volume by the pressure inside the balloon Reduction of more than 10 per cent of the resting anal pressure was recorded as an intact rectoanal inhibitory reflex.

Rectal sensation was assessed using the same rectal balloon Three parameters of sensation were recorded according to the criteria of Farthing and Lennard-Jones[9]· threshold volume, volume associated with constant rectal sensation and the volume below 400 ml at which pain became intolerable (maximum tolerable volume) In some patients a volume of 400 ml caused no apparent discomfort, but further volumes were not introduced for fear of bursting the balloon

The saline infusion test was designed to test liquid continence. A 4-channel polyvinyl catheter (external diameter 5 mm) with side openings at 2, 4, 19 and 26 cm from the anal verage was inserted into the sigmoid colon. The catheter was connected to pressure transducers and a multichannel recorder so that the pressures at 2, 4 and 26 cm from the anal verge could be recorded while isotonic saline was being infused The patient was seated on a special chair and a total of 1500 ml isotonic saline (37°C) was infused at a rate of 50 ml/min by means of a peristaltic pump (H R Flow Inducer, Watson–Marlow Ltd , UK) The patient was instructed to retain the saline for as long as possible without leakage A commode was placed under the seat to collect any fluid that leaked from the anus The volume infused at the time of the initial leak and the total volume retained were recorded Basal and peak pressure[10] were measured at 2, 4 and 26 cm from the anal verge during saline infusion

Electromyography of the pelvic floor was recorded using a concentric needle electrode Electrical activity was recorded at rest, during maximum pelvic floor contraction and during attempted defaecation

The anorectal angle, pelvic floor descent, perineal descent and anal canal length were measured from radiographs or frozen frames taken

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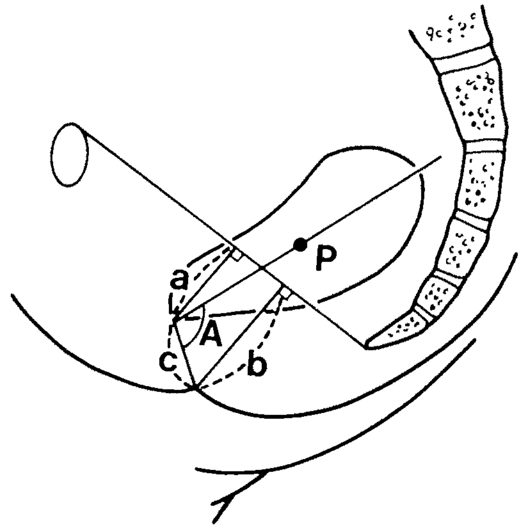

Figure 1 *Assessment of proctogram pelvic floor descent (a), perineal descent (b), anal canal length (c), centroid (P), anorectal angle (A)*

during videoproctography. The patient was seated on a lavatory pan after introducing 100 ml (120 g) of Baritop (Concept Pharmaceuticals, UK) mixed with cellulose, to achieve a consistency similar to that of normal faeces. The anorectal angle was measured as the angle between the luminal axis of the anal canal and the axis of the rectum This was assessed at rest, during maximum pelvic floor contraction and during attempted defaecation using an image intensifier linked to a video screen. The long axis of the rectum was obtained by drawing a line through the anorectal junction and the 'centroid' of the rectum. The centroid was defined as the point at which a line running from the anorectal junction could divide a lateral projection of the rectum into two equal areas. The centroid was determined by a mathematical formula programmed to analyse lateral radiographs using a BBC microcomputer. Pelvic floor descent was defined as the perpendicular distance between the pubococcygeal line and the anorectal junction The perpendicular distance between the pubococcygeal line and the anal verge was measured as perineal descent. Anal canal length was the distance between the anorectal junction and the anal verge (*Figure 1*).

Rectal emptying was assessed during videoproctography by asking the patient to evacuate as much of the introduced contrast material as possible during 1 min The result was expressed as a percentage of the amount of material infused.

As these data were not normally distributed, statistical analysis of the physiological data was made using the Mann–Whitney *U* test These studies had the approval of the local ethical committee. Patients gave consent for the studies after written explanation that any predictive parameters would allow a more rational approach for future surgical treatment The controls were studied concurrently using the same techniques

Results

The rectal prolapse was successfully controlled by rectopexy in all cases. Neither full-thickness rectal prolapse nor mucosal prolapse was observed during the 8–24 months (median, 14 months) of follow-up. Complete continence was achieved after rectopexy in six of the nine patients with incontinence Three patients remained incontinent and three patients developed constipation after the operation. Those patients who remained incontinent had a median age of 69 years (range, 61–77 years) compared with 57 years (range, 25–79 years) in those whose continence was restored.

Anal canal pressures 2 cm from the anal verge at rest, during maximum pelvic floor contraction and attempted defaecation were 50 (21–80), 79 (33–121) and 71 (36–100) cmH$_2$O (median and range) before operation and were significantly lower than in the controls in all positions (control data: at rest, 86 (53–113); maximum pelvic floor contraction, 129 (60–171); attempted defaecation, 100 (53–179) cmH$_2$O, median and range, $P<0{\cdot}005$ respectively). However, there were no significant changes after operation (*Figure 2*). Preoperative pressures 4 cm from the anal verge were significantly lower than control values during maximum pelvic floor contraction (62 (38–98) *versus* 91 (41–169) cmH$_2$O, median and range, $P<0{\cdot}005$) and attempted defaecation (77 (38–127) *versus* 112 (55–198) cmH$_2$O, median and range, $P<0{\cdot}01$) but not at rest and no significant changes were observed after operation.Pressures at 26 cm from the anal verge did not differ significantly from control values and did not change significantly after operation.

Threshold volume, volume associated with constant sensation and total tolerable volume were 100 (50–150), 200 (100–200) and 350 (200–400) ml (median and range) respectively before operation. These values did not differ significantly from control values and did not change after operation. Mean rectal compliance in patients was: 9·18 (4·29–20·00) ml/cmH$_2$O and did not differ from controls (13·15 (5·94–26·92)) or change significantly after rectopexy (7·89 (5·45–16·00)).

The rectoanal inhibitory reflex was observed in all controls but was absent in four patients with rectal prolapse. Absence of the rectoanal inhibitory reflex persisted in all four cases after successful rectopexy. Increased electromyographic activity in the puborectalis muscle was observed in 2 of 15 controls, and in 2 patients before operation. This response persisted in both patients and was observed for the first time in another patient after rectopexy.

The volume at which saline first leaked and the total tolerable volume of saline were 60 (5–1500) and 100 (0–1500) ml (median and range) respectively before operation. These values were significantly lower than controls (first leak, 800 (80–1500), $P<0{\cdot}005$; total tolerable volume, 1000 (100–1500) ml, $P<0{\cdot}005$) but did not change significantly after operation (first leak, 120 (30–1500); total tolerable volume, 120 (20–1500)). Anal canal pressures 2 cm from the anal verge during the first 5 min of the saline infusion were significantly lower than control pressures for all three parameters ($P<0{\cdot}005$) but no significant changes were observed after operation (*Table 1*). Pressures at 4 and 26 cm from the anal verge during saline infusion did not differ significantly from those of controls and did not change after operation.

Preoperative anorectal angles at rest, during maximum pelvic floor contraction and attempted defaection were 124 (109–151), 110 (91–152) and 140 (112–196) degrees (median and range) respectively. These angles tended to be more obtuse than in controls and were significantly different at rest (124 (109–151) *versus* 112 (85–134) degrees, $P<0{\cdot}05$) and during attempted defaecation (140 (112–196) *versus* 134 (88–149) degrees, $P<0{\cdot}025$). However, there were no significant changes after operation (*Figure 3*).

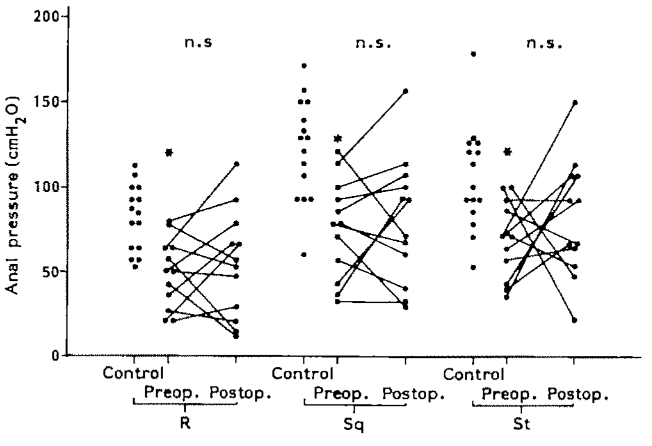

Figure 2 *Anal pressure 2 cm from the anal verge before and after rectopexy and compared with controls R, at rest, Sq, during maximum pelvic floor contraction, St, during attempted defaecation, *P<0 005, preoperative* versus *control, n.s., no significant difference observed after rectopexy*

Table 1 *Pressures at 2 cm from the anal verge during the first 5 min of the saline infusion test in controls and rectopexy patients*

			Rectopexy patients		
	Controls ($n = 15$)		Preoperative ($n = 12$)		Postoperative ($n = 12$)
Maximum basal pressure	79 (14–136)	$P < 0.005$	36 (14–50)	n.s.	43 (20–107)
Minimum basal pressure	43 (0–129)	$P < 0.005$	21 (7–43)	n.s.	29 (13–79)
Peak pressure	107 (36–193)	$P < 0.005$	64 (29–114)	n.s.	64 (36–150)

Values are median and range (cmH_2O)

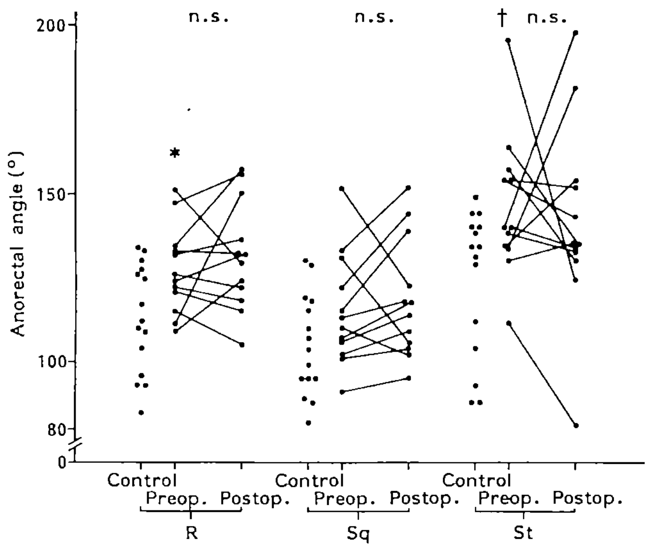

Figure 3 *Anorectal angles before and after rectopexy and compared with controls. R, at rest, Sq, during maximum pelvic floor contraction, St, during attempted defaecation,* *$P < 0.05$, †$P < 0.025$, *preoperative* versus *control, n.s., no significant difference observed after rectopexy*

Pelvic floor descent, perineal descent and anal canal length in controls and in patients before and after rectopexy are shown in *Table 2*. Preoperative anal canal length tended to be shorter in patients than in controls but this was statistically significant only during attempted defaecation ($P < 0.05$). Pelvic floor descent and anal canal length did not change significantly after operation, whereas perineal descent tended to become shorter after operation, this parameter only changed significantly during attempted defaecation ($P < 0.025$).

Percentage median rectal emptying was 83 per cent/min (range, 42–100) before operation compared with 75 per cent/min (range, 0–100) in controls ($P < 0.05$). Rectal emptying significantly decreased to 58 per cent/min (range, 0–100) after rectopexy ($P < 0.05$) when compared with preoperative levels.

When the six incontinent patients whose continence was restored were compared with the three who remained incontinent, volume at first leakage was significantly greater in patients who became continent (80 ml, range, 40–300) than in those who did not (30 ml, range, 10–40: $P < 0.025$). Preoperative median anorectal angles were more acute in patients whose continence was restored than in those who were not, the difference being statistically significant during pelvic floor contraction (*Table 3*)

Preoperative median pelvic floor descent was less in patients whose continence was restored than in those who remained incontinent, but this was statistically significant only during maximum pelvic floor contraction (*Table 4*). Preoperative median anal canal length was greater at rest and during contraction in patients who became continent than in those who did not (*Table 5*). Median perineal descent tended to be less in patients whose continence was restored in all three positions but the differences were not statistically significant

No significant differences were observed in patients whose continence was restored compared with those who remained incontinent with respect to pressures at 2, 4 and 26 cm from the anal verge, rectal sensation, rectal compliance, rectoanal inhibitory reflex, electromyography, and pressures during saline infusion or rectal emptying

Discussion

Full-thickness rectal prolapse may be successfully treated by posterior abdominal rectopexy. Despite successful treatment of the rectal prolapse, faecal incontinence persists in about a third of patients[4,6,7]. In this study three of nine incontinent patients were not improved by rectopexy. Chronic constipation is also recognized as a complication of rectopexy and three of 12 patients developed constipation in this study[11].

Physiological studies showed significant differences between patients and controls in that patients had lower anal canal pressures, earlier leakage during the saline infusion test with lower tolerable volumes, lower anal pressures during saline infusion, more obtuse anorectal angles and shorter anal canal length. These results are hardly surprising as three-quarters of the patients had associated faecal incontinence[8]. Read *et al.*[12] showed that the volume at first leak and the volume retained during the saline infusion test were significantly lower in patients with incontinence than in controls. Anorectal angles are reported to be more obtuse in incontinent patients than in controls[12,13] and we concur with these findings The rectoanal inhibitory reflex was absent in four patients, but present in all controls. Absence of the reflex has also been observed in constipated patients who do not have Hirschsprung's disease[14]. One possible reason for absence of the reflex is the low basal anal pressure especially when measured using a water-perfused catheter.

There were no significant changes in the physiological parameters that were studied after operation except for the extent of perineal descent and rectal emptying. After operation, descent decreased significantly during attempted defaecation. Decreased perineal descent may have been because of recovery of the pelvic floor muscles and the influence of rectopexy in preventing rectal descent and the associated intussusception.

The decrease in rectal emptying may have been due to improvement in continence as contrast rapidly leaked preoperatively; however there was no significant difference between the median rectal emptying in patients after operation and controls. The fact that rectal emptying is delayed after rectopexy suggests that some automatic denervation might occur following rectal mobilization.

Preoperative values for the volume at first leakage of saline, anorectal angle, pelvic floor descent and anal canal length were significantly different between patients whose continence was restored and those who remained incontinent. We accept that there is a wide scatter in some of these parameters; nevertheless,

Table 2 *Pelvic floor descent, perineal descent and anal canal length in controls and rectopexy patients*

	Control ($n=15$)	P value (control *versus* preoperative)	Rectopexy patients Preoperative ($n=12$)	Rectopexy patients P value (preoperative *versus* postoperative)	Rectopexy patients Postoperative ($n=12$)
Pelvic floor descent					
R	3·7 (1·0–7·8)	n.s.	4·0 (2·4–6·7)	n.s.	4·5 (1·9–6·7)
Sq	2·4 (0·1–7·6)	n.s.	2·6 (0·9–6·8)	n.s.	2·8 (0·5–6·0)
St	6·1 (3·2–10·7)	n.s.	7·5 (4·5–10·1)	n.s.	6·3 (3·6–8·8)
Perineal descent					
R	7·8 (5·0–10·2)	n.s.	7·0 (6·6–8·5)	n.s.	6·6 (4·8–8·5)
Sq	7·1 (4·2–10·1)	n.s.	7·2 (5·2–9·3)	n.s.	6·5 (5·6–8·8)
St	8·7 (5·9–12·0)	n.s.	8·5 (7·5–10·8)	$P<0·025$	7·1 (6·2–10·1)
Anal canal length					
R	5·0 (3·0–6·2)	n.s.	3·6 (1·2–6·2)	n.s.	3·0 (1·1–4·9)
Sq	5·6 (2·9–7·7)	n.s.	4·8 (2·6–6·8)	n.s.	4·6 (2·3–5·8)
St	3·4 (0·3–5·0)	$P<0·05$	1·6 (0·0–4·0)	n.s.	1·3 (0·4–4·0)

Data shown are median length and range (cm), R, at rest, Sq, during maximum pelvic floor contraction, St, during attempted defaecation; n.s., not significant

Table 3 Anorectal angles in patients with rectal prolapse associated with faecal incontinence

	All patients ($n=9$)	Continence improved ($n=6$)	P values (improved *versus* not improved)	Continence not improved ($n=3$)
R				
Preoperative	132 (109–151)	115 (109–134)	n.s.	147 (121–151)
Postoperative	132 (105–157)	132 (105–157)		129 (115–156)
Sq				
Preoperative	115 (91–152)	106 (91–122)	$P<0·025$	133 (131–152)
Postoperative	118 (95–152)	114 (95–144)		123 (106–152)
St				
Preoperative	140 (112–157)	138 (112–154)	n.s.	154 (135–157)
Postoperative	143 (81–198)	134 (81–198)		143 (130–154)

Data shown are median and range (degrees), R, at rest; Sq, during maximum pelvic floor contraction, St, during attempted defaecation

Table 4 *Pelvic floor descent in patients with rectal prolapse associated with faecal incontinence*

	All patients ($n=9$)	Continence improved ($n=6$)		Continence not improved ($n=3$)
R				
Preoperative	4·3 (2·4–6·7)	3·5 (2·4–4·6)	n.s.	6·3 (4·1–6·7)
Postoperative	5·3 (1·9–6·7)	5·3 (3·0–6·7)		5·3 (1·9–5·4)
Sq				
Preoperative	3·6 (0·9–6·8)	2·0 (0·9–4·3)	$P<0·05$	4·8 (3·8–6·8)
Postoperative	4·4 (1·3–6·0)	3·5 (2·5–4·7)		4·8 (1·3–6·0)
St				
Preoperative	6·6 (4·5–10·1)	5·9 (4·5–10·1)	n.s.	7·5 (6·6–8·6)
Postoperative	7·0 (5·2–8·8)	7·4 (5·4–8·8)		5·4 (5·2–7·0)

Data shown are median and range (cm), R, at rest, Sq, during maximum pelvic floor contraction; St, during attempted defaecation

Table 5 *Anal canal length in patients with rectal prolapse associated with faecal incontinence*

	All patients ($n=9$)	Continence improved ($n=6$)		Continence not improved ($n=3$)
R				
Preoperative	3·6 (1·2–6·2)	3·7 (3·6–6·2)	$P<0·05$	2·3 (1·2–3·1)
Postoperative	2·3 (1·1–4·9)	2·1 (1·1–4·9)		3·0 (2·3–3·1)
Sq				
Preoperative	4·8 (2·6–6·8)	4·8 (4·3–6·8)	$P<0·025$	3·1 (2·6–4·3)
Postoperative	4·2 (2·3–5·7)	4·1 (3·4–5·7)		5·0 (2·3–5·5)
St				
Preoperative	1·7 (0·1–4·1)	2·9 (0·3–4·1)	n.s.	1·6 (0·1–1·7)
Postoperative	1·3 (0·4–4·0)	1·1 (0·7–4·0)		1·3 (0·4–1·7)

Data shown are median and range (cm); R, at rest, Sq, during maximum pelvic floor contraction; St, during attempted defaecation even in this small cohort of patients, significant differences were detected. The parameters which predicted persistent incontinence were those usually associated in any case with more severe incontinence Some of these features, particularly abnormal descent of the pelvic floor, are thought to play an important role in the pathogenesis of idiopathic faecal incontinence[3,15] causing pudendal nerve damage to the external anal sphincter[16,17]. The importance of identifying parameters which predict patients who are likely to remain incontinent after rectopexy is that these patients might be offered a synchronous pelvic floor repair at the time of rectopexy. It remains to be seen, however, whether this policy increases the morbidity of rectopexy and whether continence might be restored by this approach. It seems likely that the only way to resolve this issue would be to randomize patients who leak saline and who have a short anal canal, obtuse anorectal angles and excessive perineal descent to receive rectopexy alone or rectopexy with pelvic floor repair We believe that the videoproctographic parameters alone will identify the patients in whom an additional postanal repair may be justified at the time of rectopexy.

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Yolanda C Oertel MD
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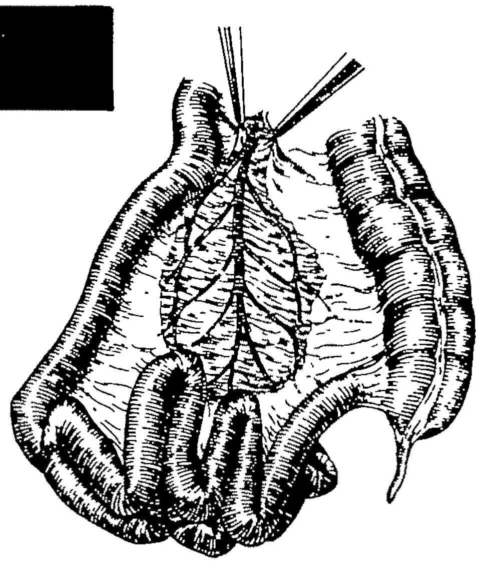

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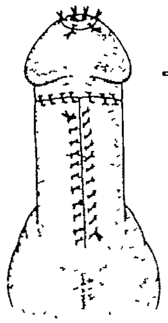

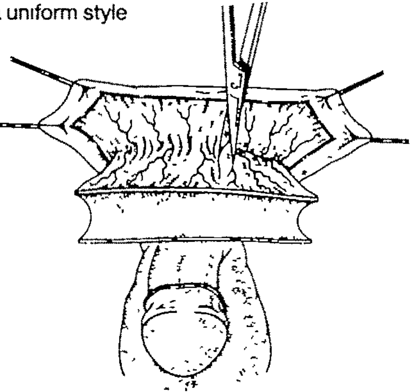

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A study of the physiological variation in anal manometry

I. Krogh Pedersen and J. Christiansen

Department of Surgery D, Glostrup Hospital, University of Copenhagen, DK-2600 Copenhagen, Denmark

Correspondence to:
Mr J. Christiansen

The physiological variation in anal manometry using a perfused catheter with radiating sideholes was studied in 78 healthy volunteers. The maximum intraindividual variation in the length of the anal high pressure zone, resting pressure and squeeze pressure was 10 mm, 26 mmHg and 68 mmHg respectively. The median 95 per cent confidence interval for length of the pressure zone was 4 mm; for resting pressure it was 15 mmHg and for squeeze pressure it was 48 mmHg. Day-to-day variation did not exceed the intraindividual variation. Constant recording with the catheter fixed in the high pressure zone revealed slow waves and ultraslow waves with amplitudes of 6–24 mmHg which could account for most of the intraindividual variation. No sex difference was found in the length of the high pressure zone whereas resting pressure and squeeze pressure were higher in men than in women. Although a tendency towards a decrease in the length of the high pressure zone, resting pressure and squeeze pressure was observed with increasing age, no significant age-related difference could be demonstrated.

Keywords: Anal incontinence, anal manometry, anal physiology

Anal manometry studies in healthy subjects are rather few and knowledge of intraindividual and day-to-day variation and of normal sex- and age-related variation is consequently limited. It has been suggested that the anal canal is shorter and the pressure is lower in women than in men, and that anal canal pressure decreases with age. Most of the data supporting these hypotheses are, however, derived from studies in patients with anorectal disease[1–3].

We present a study of intra- and interindividual variation of anal manometry as well as age- and sex-related variation in subjects with no anorectal symptoms.

Subjects and methods

A total of 58 healthy volunteers (23 men and 35 women) were studied The median age for men was 56 years (range, 30–73) and for women 53 years (range, 28–79). None had any history of gastrointestinal disease or previous anorectal surgery or were using drugs with effect on the gastrointestinal tract No bowel preparation was used.

Investigations were performed with the subject in the left lateral position with flexed knees and hips The manometric system consisted of a low-compliance open-ended perfused polyvinyl catheter with an outer diameter of 2 mm and an inner diameter of 1 mm. The catheter ended in a steel cap with the same external and internal diameter and three sideholes radiating 120°. The catheter was perfused with saline at a flow rate of 0·7 ml/min, and pressure was recorded by a water filled strain-gauge connected to a pen-recorder The manometric system had a pressure rise rate ($\Delta p/\Delta t$) of 800 mm/s.

The probe was introduced manually into the rectum and withdrawn by a machine with a constant speed of 5 mm/s. The length of the anal canal was calculated as the distance from the start of the pressure increase to the point at which pressure fell to zero when the probe left the anal canal. The maximal resting pressure was defined as the highest pressure recorded with the subject relaxed, and the maximum squeeze pressure as the highest pressure recorded during voluntary contraction of the anal sphincter Each investigation was repeated three times, and the mean value was taken as the result.

In another ten subjects (five men and five women) with a median age of 28 years (range, 21–37) anal manometry was performed ten times on the same day and from three to six times on different days at intervals ranging from 3 months to 2 years Differences were analysed by the Mann–Whitney *U* test for unpaired data.

Results

The lengths of the high pressure zone and the anal canal resting pressures and squeeze pressures are shown in *Table 1*. There was no sex difference in the median length of the pressure zone ($P > 0{\cdot}20$), whereas resting as well as squeeze pressures were significantly higher in men than in women ($P < 0{\cdot}05$).

The effect of age on the length of the high pressure zone and on resting pressure and maximal squeeze pressure was studied in subjects ≤50 years, 51–60 years and >60 years (*Table 2*) There was a trend towards decreasing values with increasing age, but no significant difference could be demonstrated. The sex difference in resting pressure and squeeze pressure was found in all age groups.

The intraindividual variation based on ten measurements performed on the same day is shown in *Table 3*. The largest individual variation in the length of the pressure zone was 10 mm, in resting pressure 26 mmHg and in squeeze pressure 68 mmHg. The median 95 per cent confidence interval for the length of the pressure zone was 4 mm, for resting pressure 15 mmHg and for squeeze pressure 48 mmHg

Table 4 shows the time-related intraindividual variation in the length of the pressure zone, resting pressure and squeeze pressure from three measurements performed over a period ranging from 3 to 24 months. The 95 per cent confidence interval

Table 1 *The influence of sex on the length of the anal high pressure zone, resting and squeeze pressures*

	Women	Men
Length of high-pressure zone (mm)	22 (22–38)	28 (21–37)
Maximum resting pressure (mmHg)	46 (40–58)	60 (51–98)
Maximum squeeze pressure (mmHg)	103 (78–190)	163 (76–234)

Values are median and 95 per cent confidence intervals

Table 2 *The effect of age on the length of the anal high pressure zone, resting and squeeze pressures*

	<50 years (*n*=20)	51–60 years (*n*=22)	>60 years (*n*=16)
Length of high pressure zone (mm)	31 (24–36)	28 (21–42)	26 (18–40)
Maximum resting pressure (mmHg)	68 (40–100)	56 (28–100)	46 (22–88)
Maximum squeeze pressure (mmHg)	160 (70–240)	158 (64–240)	150 (56–210)

Values are median and range

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Table 3 *Intraindividual variation in length of anal high pressure zone, resting and squeeze pressure*

Subject	Length of pressure zone (mm)	Resting pressure (mmHg)	Squeeze pressure (mmHg)
1	40 (36–40)	66 (54–80)	200 (190–240)
2	40 (36–44)	57 (46–70)	240 (232–260)
3	42 (36–44)	61 (54–70)	192 (180–200)
4	41 (40–44)	77 (76–90)	254 (220–288)
5	39 (35–44)	68 (64–80)	215 (180–242)
6	35 (30–40)	51 (50–68)	254 (220–288)
7	35 (32–36)	48 (40–50)	120 (118–122)
8	32 (30–34)	50 (44–56)	216 (180–248)
9	37 (30–40)	72 (60–80)	100 (92–104)
10	38 (34–43)	66 (61–76)	200 (158–220)

Values are median and range of ten investigations in ten subjects performed on the same day

Table 4 *Time-related intraindividual variation in ten subjects based on three measurements performed over a period ranging from 3 to 24 months*

Subject	Length of pressure zone (mm)	Resting pressure (mmHg)	Squeeze pressure (mmHg)
1	41 (39–43)	74 (66–76)	210 (190–240)
2	35 (24–40)	48 (44–57)	244 (232–260)
3	39 (36–41)	79 (61–98)	191 (180–204)
4	40 (38–42)	81 (78–89)	254 (220–288)
5	39 (37–40)	68 (54–75)	223 (180–300)
6	40 (38–41)	82 (80–88)	254 (220–288)
7	32 (28–33)	56 (52–64)	120 (120–120)
8	34 (28–40)	80 (69–95)	216 (180–248)
9	33 (28–40)	57 (51–60)	99 (92–104)
10	38 (35–41)	70 (61–86)	198 (150–232)

Values are median and range

of these measurements was compared with the 95 per cent confidence interval of the measurements performed on the same day in the same subject by a Wilcoxon test; no significant difference was demonstrated, indicating that the day-to-day variation is no greater than the intraindividual variation.

Table 5 shows the result of continuous registration of spontaneous pressure changes in the anal canal during 10 min with the catheter fixed in the middle of the high pressure zone Two characteristic curves were seen· one was due to slow waves with a frequency of 0·20–0·38 and an amplitude of 6–20 mmHg, and the other to ultraslow waves (in nine of the ten subjects) with a frequency of 0·008–0·016 Hz and an amplitude of 9–24 mmHg. This variation may account for most of the observed intraindividual variation, although a certain effect of voluntary contraction cannot be ruled out.

Discussion

The accuracy of the manometric system cannot be assessed under realistic biological circumstances. Likewise it is not possible to separate the intraindividual variation studied here into 'pure' intraindividual variation and variation due to the precision (reproducibility) of the manometric system By using low compliance catheters and by withdrawing the catheters with constant speed, precision of the recording system is probably maximal, and accounts for only a fraction of the intraindividual variation found in this study.

The fact that variation between measurements in the same individual at different times was of the same magnitude as the intraindividual variation suggests that day-to-day variation is insignificant, which is an important factor in clinical practice especially when measurements are performed over a period of time to evaluate the effect of a given treatment.

The intraindividual variation in length of the high pressure zone, resting pressure and squeeze pressure was somewhat higher than that reported in a study on profilometry using microtransducers[4]; these results were, however, based on only three measurements in each subject. The results of the present study indicate that most of the intraindividual variation in anal canal pressure may be explained by slow and ultraslow waves, indicating that changes in resting anal pressure of approximately 20 per cent must be considered within the physiological range. This is true also for measurements performed at different time intervals. The amplitude of the ultraslow waves was almost the same as that of the slow waves, which is in contrast to other reports where ultraslow waves were found to have a much larger amplitude[5]. A few studies have evaluated sex differences in the length and pressure profile of the anal canal. Nivatvong *et al.*[6] studied the surgical length of the anal canal, defining it as the distance from the anal verge to the anorectal ring, measured with the right index finger; as in the present study no sex difference was found. Taylor *et al* [1] found only a slight, non-significant sex difference in anal canal pressure, whereas Read *et al.*[2], as in the present study, found a significantly higher pressure in men than in women, indicating the necessity of sex-matched control subjects. Unlike these and other investigators[2,7] we found no significant decrease in anal canal pressure with increasing age in asymptomatic subjects; it should be stressed, however, that only four subjects were >70 years old.

In conclusion, this study shows that intraindividual variation in anal canal pressure for the greater part may be explained by slow wave and ultraslow wave pressure changes normally occurring at rest, and that the day-to-day variation is within the range of these spontaneously occurring pressure variations. The importance of giving the patients some time to relax before each investigation should be stressed; this is in order to minimize the effect of voluntary contractions. Furthermore, both resting and squeeze pressures were higher in men than in women whereas no sex difference in the physiological length of the anal canal and no relationship between age and anal canal pressure was found.

Table 5 *Result of continuous pressure measurement in the anal canal during 10 min*

	Slow waves		Ultraslow waves	
	Frequency (Hz)	Maximum amplitude (mmHg)	Frequency (Hz)	Maximum amplitude (mmHg)
1	0·25	18	0·011	12
2	0·35	14	0·008	10
3	0·21	20	0·012	24
4	0·31	14	0·010	20
5	0·38	6	0·012	10
6	0·20	14	0	0
7	0·22	10	0·016	12
8	0·31	12	0·011	14
9	0·28	08	0·010	9
10	0·30	11	0·011	21

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For debate

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Treatment of cancer of the colon: a non-specialist's point of view

A. Marston

The Middlesex Hospital, Mortimer Street,
London W1N 8AA, UK
Correspondence to: Mr A. Marston

A few months ago I operated on a man with a carcinoma of the left colon who also had three polyps in the transverse colon and the caecum, one of which was 2 cm in diameter. I carried out a subtotal colectomy and ileorectal anastomosis, a straightforward operation from which my patient made a good recovery. Examination of the specimen confirmed a Dukes' B carcinoma of the sigmoid colon, and three benign polyps. He now reports back to the outpatient department, very well, but having between two and five loose bowel motions each day.

Supposing that this patient had had the cancer but not the polyps, would there be a case for doing the same operation? After all, the entire colonic mucosa is a potential malignant field whether or not polyps are present. Consider the advantages of carrying out a sub-total colectomy and ileorectal anastomosis for every 'curable' cancer, wherever situated:

1. The operation is simple and the anastomosis is made between areas of bowel which have an abundant blood supply and which can be brought together without tension, thus minimizing the risk of anastomotic leakage, peritonitis and fistula development. No drain is needed.

2. There is a high incidence of recurrent colonic cancer following partial colectomy because of synchronous or metachronous tumours, polyps which are missed at colonoscopy or laparotomy and suture-line recurrences implanted at the time of surgery. Removal of the entire mucosal field would eliminate this problem. After all, partial cystectomy for carcinoma of the bladder is a thing of the past, and surgery for oesophageal tumours is tending more and more towards total removal of the organ, with anastomosis at a safe and accessible level.

3. Traditionally, after an operation for colonic cancer the patient is 'followed up' for 5 years, or sometimes for life. This usually means that he sees a different registrar every 6 months, who looks at the steadily thickening folder, conducts a quick physical check, and gives reassurance. Effective follow-up requires a careful examination of the colon, either by barium enema or fibreoptic colonoscopy. However if the colon has been removed, this can be achieved by a digital examination and passage of a rigid instrument, both of which are within the compass of a relatively inexperienced surgeon.

4. Colorectal surgeons have spent much time, effort and money on the detection of recurrences, and the identification of tumour markers is an expensive and cumbersome process. It remains to be seen whether a rise in carcinoembryonic antigen level above the baseline (which may or may not imply residual tumour) should lead to a further operation. The rescue rate which surgery achieves in such cases is, I suspect, exceedingly low.

Supposing we brought in a policy of subtotal colectomy and ileorectal anastomosis for every case of colonic cancer, what price would our patients pay? The function of the colon is to absorb water and its loss results in a varying degree of diarrhoea and frequency which cannot always be controlled by diet and drugs. Obviously an elderly patient with lax sphincters might be crippled by such surgery, but the life expectancy in this age group is determined by many factors other than that of colonic cancer, and common sense would indicate where the operation was inappropriate. No overall surgical policy is applicable to every patient and the procedure must be adapted to individual needs. For my own part, if I had a carcinoma of the colon, I think I would wish to have the whole organ removed and an ileosigmoid anastomosis. I would rather be loose and living than constipated and dead. Comments are awaited from colleagues in coloproctology.

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72–75

Air-filled microballoon manometry for use in anorectal physiology

R. Miller,
D. C. C. Bartolo,
D. James* and
N. J. McC. Mortensen

Department of Surgery, Bristol Royal Infirmary, Bristol, and
**Department of Clinical Measurement, Royal Devon and Exeter Hospital, Exeter, UK*
Correspondence to:
Mr R. Miller, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

Manometry is fundamental to anorectal physiology but the water-filled manometric systems commonly used have several disadvantages. To investigate the 'new' air-filled microballoon system, we compared it with a standard water-filled equivalent by measuring sphincter length, maximum resting pressure (MRP) and maximum voluntary contraction pressure (MVC) in 44 patients using the station pull-through technique. A good correlation was found for all three parameters (Spearman correlation coefficient r_S*: sphincter length = 0·86, MRP = 0·86 and MVC = 0·94,* $P < 0{\cdot}001$*). Repeat studies in 15 patients showed excellent reproducibility (*r_S*: sphincter length = 0·97, MRP = 0·96 and MVC = 0·97,* $P < 0{\cdot}001$*). Air-filled microballoon manometry gives results similar to a water-filled microballoon system and has many advantages.*

Keywords: Anorectal manometry

The most basic investigation in the field of anorectal physiology is the measurement of anal sphincter length and pressures. Most manometric systems use a pressure sensitive device in the anorectum connected to an external transducer by indistensible water-filled tubing[1–3]. The output from the transducer is then amplified and recorded on a chart recorder. Such an arrangement is prone to artefacts produced by movement of the tubing. It has to be zeroed at the anal verge and care taken to ensure that there are no air bubbles in any part of the system.

Air-filled manometry avoids these problems and, while it has been used in the past, the catheters have tended to be cumbersome, and the results have not been compared with water-filled equivalents[4–6]. This study was undertaken to determine whether an air-filled system that has been successfully used in the urogenital tract[7] was suitable for use in the anorectum.

Patients and methods

In all, 44 patients were studied, 18 men and 26 women, median age 58·5 (range 24–83) years. They consisted of 6 normal subjects, 15 patients with faecal incontinence, 7 with constipation, 3 with haemorrhoids and 13 with miscellaneous anorectal complaints. A detailed history using a standard questionnaire was obtained from each patient with special reference to anorectal complaints. This was followed by a digital examination of the rectum. No bowel preparation was used and the patients were studied in the left lateral position.

The water-filled system consisted of a 6 mm microballoon (Bristol Dippings Ltd., Bristol, UK) mounted on a ureteric catheter, external diameter 1·5 mm (*Figure 1*). This was connected to an external transducer (Statham P23Gb, Spectromed, Coventry, UK) via 1 m of indistensible tubing. The output was amplified and recorded by a multichannel pen recorder (Hewlett-Packard 7758A, Massachusetts, USA).

The balloons for the air-filled system were made by coating thin latex on a variety of stainless steel formers. A variety of shapes and sizes were tried, the final dimensions being 10 mm long and 5 mm in diameter: it was made by Dipped Latex Products, Gloucestershire, UK (*Figure 1*). It was connected via capillary tubing 30 mm long (internal diameter 0·7 mm, external diameter 2 mm) to a Druck PDCR75 transducer (Ormed Engineering, Welwyn Garden City, UK). The transducer cap was modified to reduce the 'dead' space in the system by filling it with high density plastic and drilling a hole through the centre to allow communication between the catheter and the pressure sensitive membrane of the transducer (*Figure 2*). The cap also had an 'O' ring fitted to the inside to provide an air seal. The transducer output was amplified and recorded by a Dantec 21C15 amplifier and System 2100 pen recorder (Dantec Electronics, Bristol, UK). The balloon was partially deflated when used to prevent any increase in

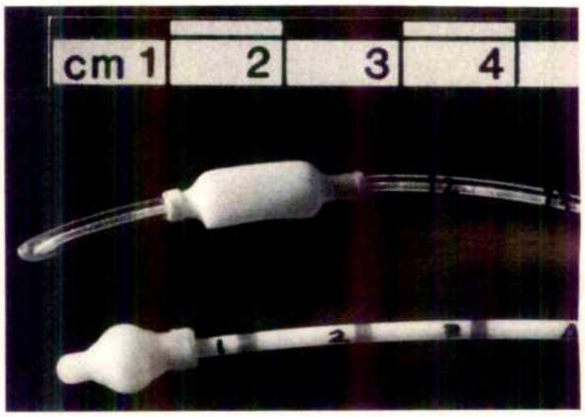

Figure 1 *The air-filled (above) and water-filled (below) microballoon catheters*

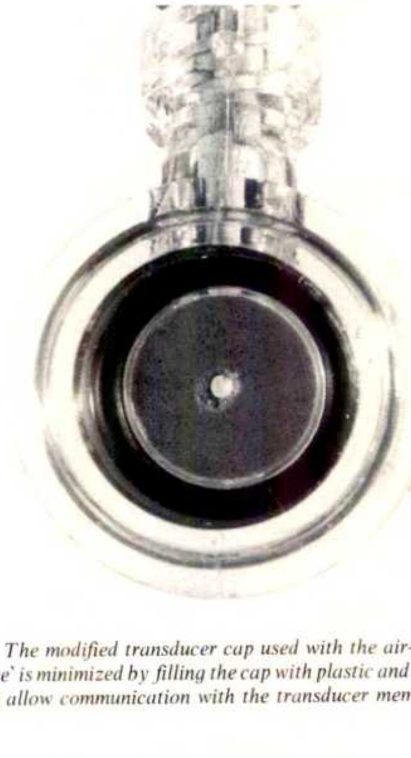

Figure 2 *The modified transducer cap used with the air-filled catheter. 'Dead space' is minimized by filling the cap with plastic and a hole is drilled through to allow communication with the transducer membrane*

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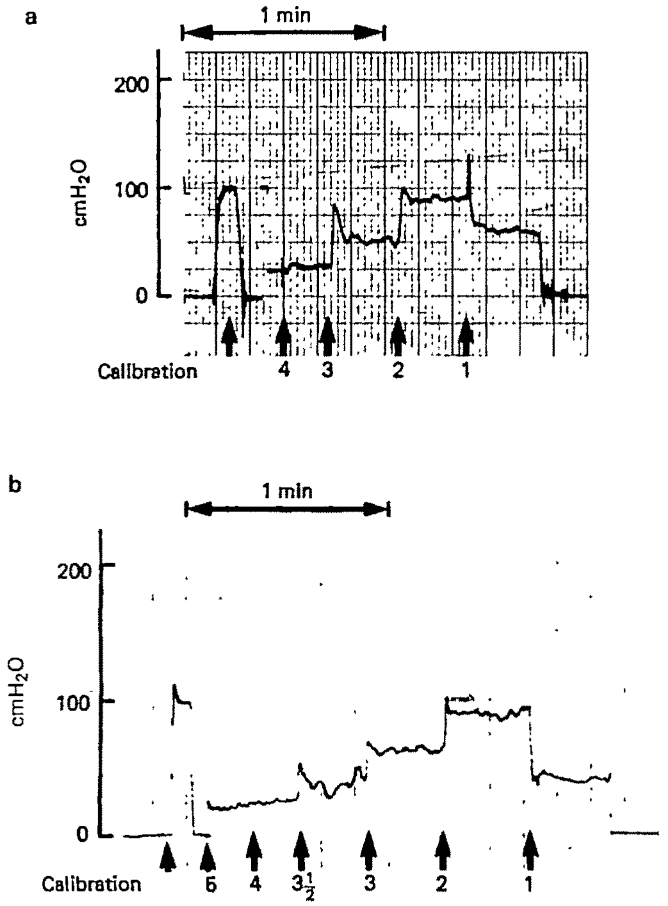

Figure 3 *Traces of resting sphincter profile from the same patient,* **a** *using water-filled and* **b** *with air-filled manometry*

pressure owing to warming of the air on insertion into the rectum. Calibration to 400 cmH$_2$O was possible using a pressurized glass container connected to a mercury sphygmomanometer The microballoon was placed in the jar with a split rubber bung round the catheter maintaining the air seal. The pressure was then increased to 100 cmH$_2$O for calibration which was performed before each study The same arrangement was also used to determine the range over which the system gave a linear response per unit rise in pressure.

The station pull-through technique was used to assess sphincter length and pressures. The catheter was inserted 7–8 cm into the rectum and a mark made at the anal verge from which all subsequent measurements were made. It was then withdrawn, initially at 0·5 cm stations until the high pressure zone was reached and the distance of this point from the verge was taken as the sphincter length. The pressure at rest was then recorded at 1 cm stations from the anal verge, the highest of which was called the 'maximum resting pressure' (MRP) (*Figure 3*). This was repeated with the patient squeezing the sphincter tight at each station to obtain the 'maximum voluntary contraction pressure' (MVC). The whole procedure was repeated on the same day in 15 patients to assess reproducibility

Statistical analysis

The correlation between techniques and reproducibility of the air manometric system were assessed using the Spearman ranked correlation coefficient. In addition, the graphical technique using the difference of the means as described by Bland and Altman[8] was also used both to compare the systems and to determine whether the two could be used interchangeably. All figures quoted are medians with the range in parentheses

Results

The air-filled system produced a linear recording of pressure up to 400 cmH$_2$O Above this an increase in pressure was recorded but with progressively smaller deflections per unit of pressure rise. The results of sphincter length, MRP and MVC for the water-filled manometry were 3·5 cm (2–4·5), 85 cmH$_2$O (25–220) and 180 cmH$_2$O (55–560) while those from the air-filled system were 4 cm (2–5), 70 cmH$_2$O (15–170) and 170 cmH$_2$O (65–460) respectively. The Spearman correlation coefficient between these techniques for sphincter length, MRP and MVC was 0·86, 0·86 and 0·94 respectively ($P < 0{\cdot}001$) (*Figure 4a, b* and *c*). Using the difference of the means method it was evident that the two systems were not interchangeable as the value for two standard deviations (2 s.d.) of sphincter length, MRP and MVC were 0·72 cm, 40 cmH$_2$O and 85 cmH$_2$O respectively (*Figure 5a, b* and *c*).

Reproducibility using the air system as assessed by the Spearman correlation coefficient was excellent, being $> 0{\cdot}96$ for each parameter ($P < 0{\cdot}001$). This was also the case using the difference of the means method where 2 s.d. for sphincter length, MRP and MVC were 0, 10 and 20 cmH$_2$O respectively.

Discussion

There are many available methods for measuring anorectal pressure which make comparison between centres difficult, and which occasionally produce conflicting results[1–6,9–12]. Water-filled systems are most commonly in use, either employing perfused catheters or microballoons as used in this study. Each has its own particular advantages and disadvantages and none appears to be accepted as the 'gold standard'. Perfusion manometry measures 'yield' pressures[13] and requires rather bulky equipment but it is relatively easy to make multilumen

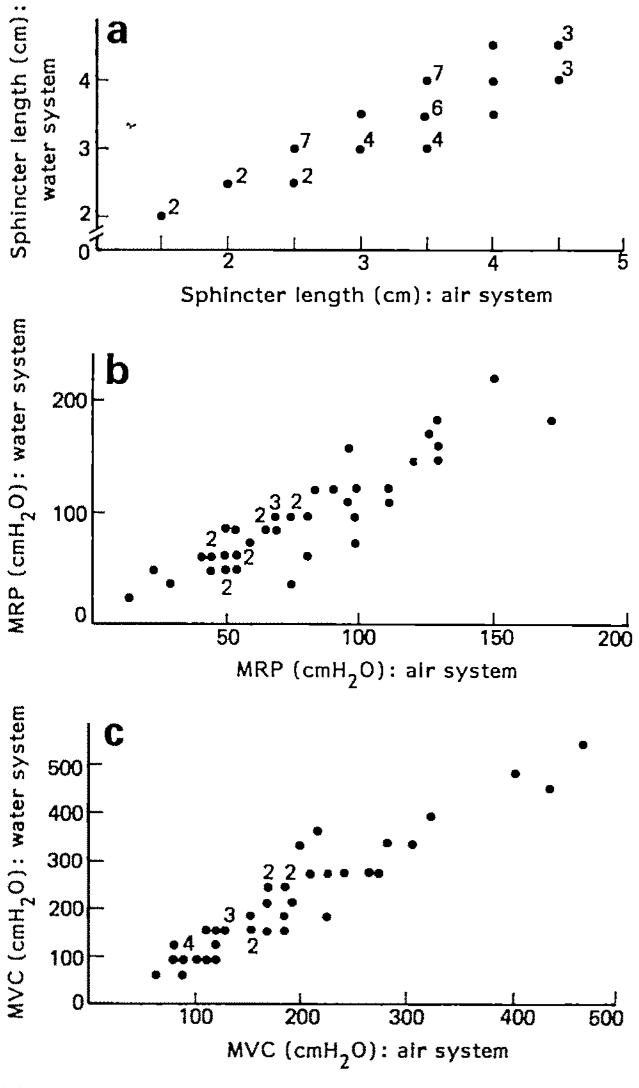

Figure 4 *Spearman ranked correlation of* **a** *sphincter length,* **b** *MRP and* **c** *MVC using the two systems. MRP, maximum resting pressure, MVC, maximum voluntary contraction pressure,* $r_s = 0{\cdot}86$, *0 86 and 0 94 respectively,* $P < 0\ 001$ *for each correlation*

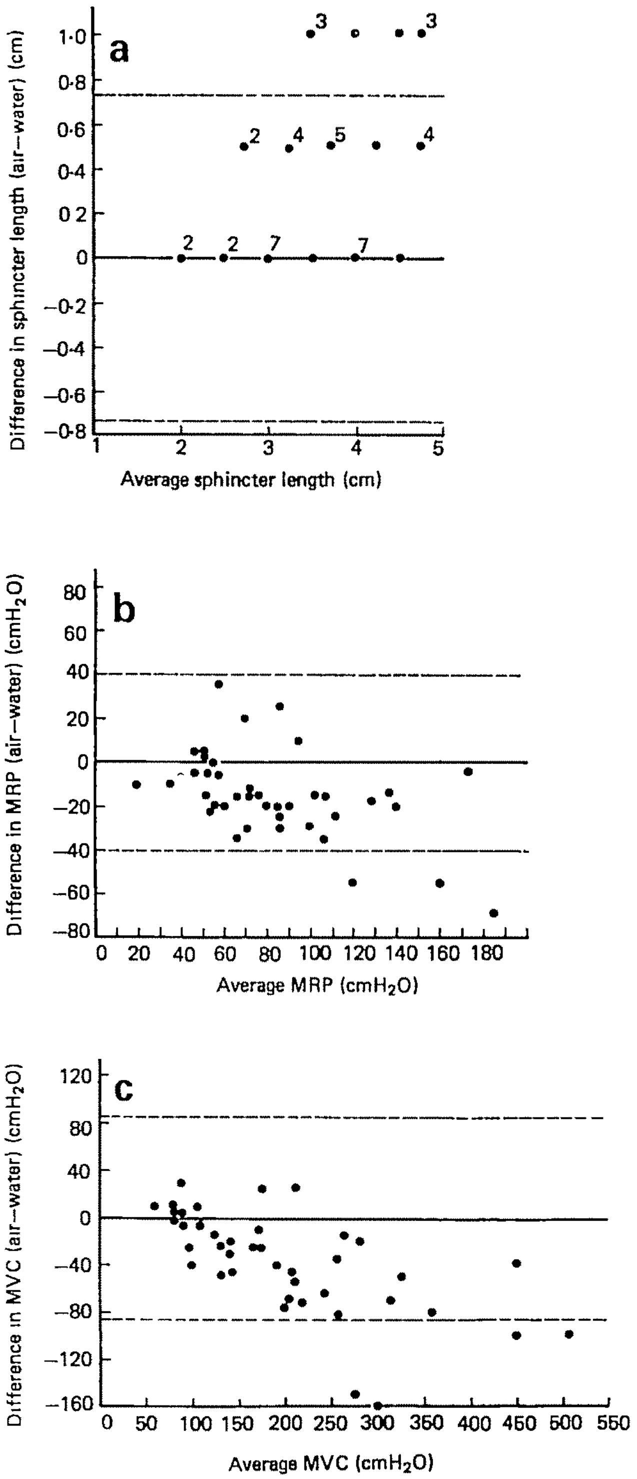

Figure 5 *Correlation of water- versus air-filled manometry using differences of the mean* **a** *sphincter length* **b** *MRP and* **c** *MVC. The sphincter length was in general longer when measured with the air-filled system Using this analysis it is evident that the degree of correlation does not permit the interchangeable use of the two systems. MRP, maximum resting pressure, MVC, maximum voluntary contraction pressure, ——, mean, –––, ±2 s d*

catheters for measuring pressures from several discrete points in the gut[1]. Microballoon assemblies tend to be larger in diameter and as the sphincter responds to distension by contracting they record higher pressures[14,15]. Both must be free from air bubbles, are very prone to artefacts due to movement of the connecting tubing and have to be zeroed at the anal verge before each study. For these reasons they would be entirely unsuited to, for example, manometry in conjunction with radiological studies or with ambulatory subjects[16]

The more recent advent of microtransducer catheters has provided an alternative to using an external transducer[10] They have the advantage of simplicity in use and, being of narrow diameter, they minimize disturbance to the sphincter. We have compared these catheters using the station pull-through technique with water-filled microballoons and have shown their limitations due to the directional nature of the sensing membrane and radial variation in anal canal pressure[17]. Furthermore, these catheters are much more expensive than those employing an external transducer

Any new system, therefore, must possess definite advantages over those currently available. We believe that, at the risk of further confusion to the literature, air-filled manometry is a good alternative. The pressures correlate well with water-filled manometry, and it is simple to set up as any conventional external transducer can be modified to take the air catheter. These modifications are designed to reduce the dead space between the microballoon and the transducer so that pressure changes are transmitted directly to its sensitive membrane. The catheters themselves are easy to construct and use and precautions to exclude air bubbles are obviously unnecessary. Zeroing is achieved simply by pressing the appropriate button on the amplifier and is independent of the height of the catheter or transducer. Furthermore, they are free from any artefact due to movement of the catheter or its connecting tubing. If required, multilumen catheters can be constructed using lengths of capillary tubing protected by an outer catheter.

The sphincter length was longer using the air system than that recorded using water-filled balloons but this is to be expected as the balloon itself was 1 cm long. The advantage of a longer balloon however outweighs this problem, which could be corrected for in use. The longer balloon results in an average pressure from a zone of the anal canal to be recorded, thereby minimizing error due to radial and longitudinal variation in anal canal pressure[18] to which side hole perfused systems and microtransducer catheters are prone[17].

The sphincter pressures were in general lower when recorded by the air system. This is probably due to the smaller diameter balloon used in the air-filled system. It is unlikely that these differences in pressure were owing to the differences in the transducers, amplifiers and pen recorders used as both systems had similar filter settings and recorded linear increases in pressure up to 400 cmH_2O The differences between the recorded pressures, however, did mean that the two systems could not be interchanged, and therefore any longitudinal study would require the exclusive use of one or other technique.

Air balloons do require the transducer to be reasonably close to the patient as long lengths of connecting tubing increase the dead space and therefore reduce the range over which the system gives linear results for a given pressure change In our unit the transducers are not fixed in any way and lie on the bed during the studies. In situations where the patient is more mobile, for example if manometry is combined with radiology, they can easily be attached to the patient's waist.

In conclusion, air-filled microballoon manometry offers many advantages over water-filled systems for routine anorectal investigation and is inexpensive and easy to use.

Acknowledgements

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Case report

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Pre-treatment with octreotide as an adjuvant to surgical resection in Zollinger–Ellison syndrome

A. N. Kingsnorth, D. A. Gould* and B. Rodgers†

*Departments of Surgery, *Radiology and †Pathology, Broadgreen Hospital, Liverpool, UK*

Correspondence to: Mr A N. Kingsnorth, University of Liverpool, Department of Surgery, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

Case report

A 57-year-old nursing auxiliary presented in October 1986 with a 5-month history of passing up to 10 watery stools daily. After barium enema a diagnosis of irritable bowel syndrome was made and treatment with mebeverine hydrochloride temporarily relieved the symptoms In June 1987 the patient was admitted urgently with acute abdominal pain and vomiting. Her bowel frequency had increased to 15–20 stools daily Air-fluid levels were present on a plain abdominal film and symptoms failed to settle with conservative treatment.

At laparotomy a penetrating transmural jejunal ulcer was present 6 cm from the duodenojejunal flexure There was a 10 cm mass in the head of the pancreas and transduodenal Trucut biopsy revealed acute pancreatitis A diagnosis of gastrinoma in the head of the pancreas causing small duct obstruction and resulting in localized pancreatitis and jejunal ulceration was made The ulcer was oversewn and the abdomen closed Postoperative serum gastrin was 377 µmol/100 ml (reference range 10–30). Initial treatment with ranitidine (300 mg t.d s.) did not control diarrhoea and only partially resolved dyspeptic symptoms. Gastroscopy revealed massive post-bulbar ulceration as far as the endoscope would reach. Acid output studies showed a basal acid secretion of 27 mmol/h (normal range 0–6), and a maximal acid output of 110 (normal range 8–40). Pituitary fossa X-rays (to exclude multiple endocrine neoplasia syndrome) were normal Ultrasound scan of liver, computed tomography scan of liver and pancreas, and endoscopic retrograde cholangiopancreatography were normal Coeliac axis arteriogram showed a blush between the posterosuperior and anterosuperior pancreaticoduodenal arteries with early filling of an adjacent enlarged vein suggestive of tumour circulation.

One month before planned definitive surgery treatment was begun with octreotide 50 µg b d (subcutaneously) and within hours there was complete symptomatic relief. Serum gastrin levels were reduced (*Figure 1*) and basal acid output fell to 2·8 mmol/h. Repeat gastroscopy after 3 weeks therapy showed complete healing of jejunal ulceration

At the second laparotomy pancreaticoduodenectomy was performed with a separate Roux loop for the pancreatic anastomosis[1] (*Figure 2*). Serum gastrin measured 2 days after surgery was 22 µmol/100 ml (*Figure 1*). Histological examination of the resected specimen showed a completely resected islet cell tumour in the head of the pancreas with nodal metastases Postoperative recovery was uneventful At recent follow-up the patient is asymptomatic, takes no drug therapy and serum gastrin levels are within the normal range

Discussion

The surgical treatment of patients with non-metastatic gastrinoma is controversial. In some centres the preferred treatment is total gastrectomy combined with enucleation of easily accessible primary tumours[2–4]. The only patients cured in this way are those in whom a solitary tumour has been completely enucleated or in whom a duodenal wall tumour has

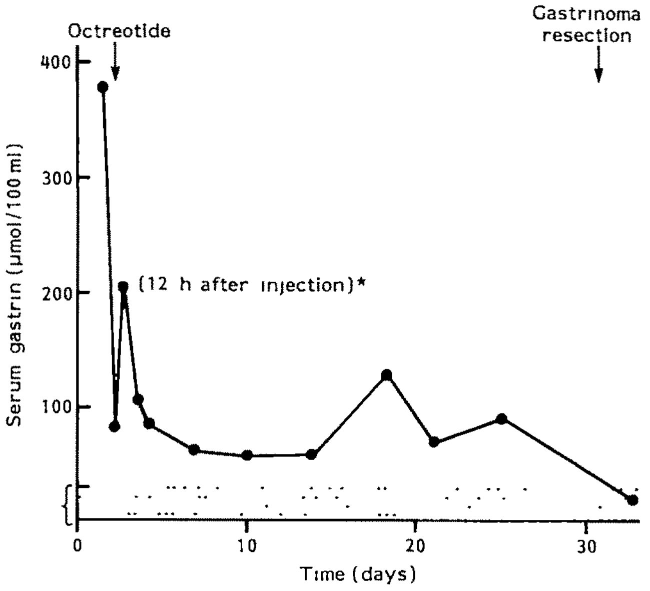

Figure 1 *Serial pre-operative and postoperative gastrin levels Treatment began with octreotide, given at a dosage of 50 µg b.d subcutaneously *All other serum measurements were taken within 4–6 h of octreotide injection*

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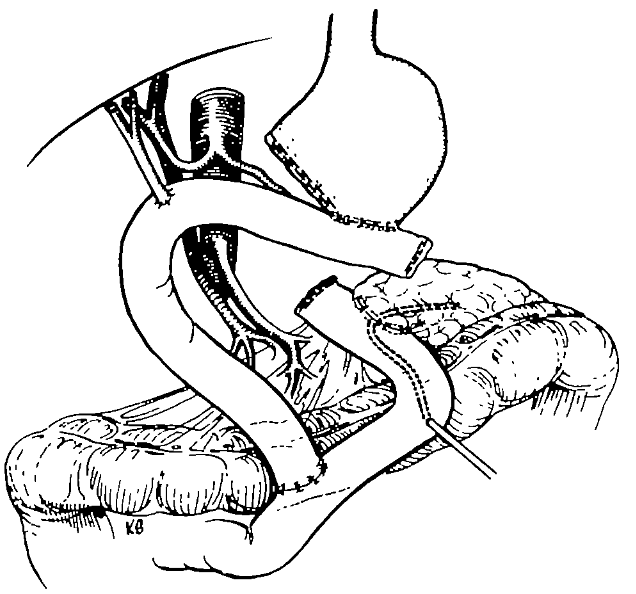

Figure 2 *Method of anastomotic reconstruction after Whipple-type resection*[1]

been incidentally removed with the gastrectomy specimen. Cure, defined as a decrease in the gastrin levels to the normal range within 48 h of surgery, occurs in approximately 15 per cent of patients and the 10-year life-table survival rate is 50 per cent[5]. A more radical approach involving pre-operative imaging techniques with ultrasound and CT scanning combined with portal venous sampling to localize pancreatic primary tumours can increase the resectability rate[6]. In experienced hands with this approach the cure rate can increase to between 20 and 30 per cent with no operative mortality[6,7]. We adopted this latter approach with a view to curative resection and since octreotide can ameliorate experimentally induced acute pancreatitis[8], we hoped that the localized pancreatitis in our patient would resolve.

Ellison and colleagues have recently reported 10 patients with the Zollinger–Ellison syndrome treated with subcutaneous octreotide[9]. Serum gastrin levels were reduced and gastric acid secretion was almost completely inhibited for 18 h after a single 100 μg subcutaneous injection. Similar reductions in serum gastrin and acid secretion were achieved in our patient with complete symptomatic relief. Pre-operative treatment with octreotide requires further evaluation in the management of patients with Zollinger–Ellison syndrome suitable for surgical resection.

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Experience of restorative proctocolectomy with ileal reservoir

W. G. Everett

Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, UK

Correspondence to:
Mr W. G. Everett

The experience gained with restorative proctocolectomy and ileal reservoir in 60 patients is presented. Fifty-two patients had W reservoirs and the operative technique of the procedure is described in detail. Forty patients had a defunctioning ileostomy and 20 had a single stage procedure. There was no perioperative mortality. The main complications were sepsis (28 per cent), intestinal obstruction (18 per cent) and reservoir ileitis (20 per cent). There was a significant improvement in sepsis rate (from 20 to 4 per cent) and hospital stay (from 31·8 to 15·6 days) with increased experience. The functional results of 48 patients with W reservoirs was assessed. The mean number of evacuations per 24 h (±s.d.) was 3·8 ± 0·2. Sixty-five per cent of patients did not evacuate at all, or rarely, at night and none evacuated more than once at night. Forty-four per cent of patients took antidiarrhoeal agents. Continence was normal in 50 per cent of patients. Minor leakage occurred in 46 per cent of cases, frequent leakage in 4 per cent and incontinence in none. Sexual function in 29 men was normal. Ninety-four per cent of patients considered the result of their operation to be good or excellent.

Keywords: Restorative proctocolectomy, ulcerative colitis, familial adenomatous polyposis

The first restorative proctocolectomy with ileal reservoir was performed by Sir Alan Parks in 1976 and a report of five cases was published 2 years later[1]. Although several hundreds of these operations have been carried out in the USA[2–4], the experience in this country has been much smaller and even in some large centres the operation is not performed. As the number of publications from the UK is small there is a need for more data and the results from one unit in Cambridge are therefore reported.

Parks *et al.* in their original description of the operation used a three-loop S reservoir but it was found that only half the patients could void spontaneously, the remainder needing to use a catheter[5]. It was subsequently shown that the problem in emptying was related to the length of the distal ileal segment[6] and if this was kept short this difficulty was largely overcome[7]. Evacuation occurs spontaneously with a two-loop J reservoir as this provides dependent emptying and completely avoids the distal ileal segment[8]. This type of reservoir is however associated with increased frequency of emptying which is probably the result of a smaller capacity. With a view to overcoming this problem Nicholls designed a four-loop W reservoir with a greater capacity and no distal ileal segment[9]. In 1984 the author, independently of Nicholls and Lubowski, designed a very similar four-loop reservoir. The operative technique is presented together with the complete experience of restorative proctocolectomy in one centre.

Patients and methods

Patients

Between December 1979 and February 1988, 60 restorative proctocolectomies were performed. The first six were S reservoirs, there was then one J reservoir and the remaining 53 were W reservoirs. There were 33 men and 27 women operated on (male:female ratio, 1·2:1). Ages ranged from 18 to 65 years (mean age 33·9 years). Four patients were over the age of 50 years.

Fifty patients had inflammatory bowel disease, of whom two were subsequently found to have Crohn's disease in spite of the most careful preoperative review of the pathology, radiology and clinical course. Ten patients had familial adenomatous polyposis. In four cases there was an associated large bowel carcinoma: two with ulcerative colitis had neoplasms of the caecum and upper rectum and two with familial adenomatous polyposis had splenic flexure and sigmoid growths.

Methods

Preoperative preparation. The patient is put on a fluid diet for 24 h before operation to ensure that the small bowel contains no food matter. If a colectomy has not previously been performed the bowel is prepared with sodium picosulphate (Picolax®, Nordic Pharmaceuticals Ltd., UK). If a colectomy has already been carried out the rectal stump is washed out.

The abdominal dissection. The patient is catheterized and placed in the Lloyd-Davis position. The abdomen is opened through a long left paramedian incision.

The dissection is begun by incising the peritoneal reflection on the left of the sigmoid mesentery. The ureter is identified and pushed posteriorly. The peritoneum on the right aspect of the mesosigmoid is then incised and the distal part of the vascular pedicle containing the inferior mesenteric vessels is ligated in continuity and divided. The mesosigmoid is then lifted forwards off the aorta and the dissection carried downwards into the pelvis keeping close to the mesentery. The hypogastric nerves are then clearly seen as two strands lying posteriorly beneath the pelvic fascia at the level of and inferior to the lumbosacral disc. (Their preservation is of great importance in male patients.) The pelvic peritoneum is then divided on either side of the rectum and across the midline as low as possible. The dissection is continued posteriorly between the mesorectum and the presacral fascia. This plane is clearly defined and the pelvic fascia should not be breached. Scissor dissection is used throughout and blunt dissection with a swab on a holder is avoided as this may damage the pelvic nerves. The lateral ligaments are then divided as close as possible to the rectal wall. The rectum is now fully mobilized and a Hayes' clamp is placed across the bowel just above the intended site of division. An assistant then washes out the rectal stump with water until it is completely clean. A sigmoidoscope is inserted so that any fluid can be sucked out and the distance of the clamp from the anal verge measured. The aim is to divide the rectum 7–8 cm above the anal margin. This is done with diathermy, taking care to coagulate any blood vessels so that following removal of the rectum the pelvis is absolutely dry.

The colectomy then proceeds in the standard manner with preservation of the omentum. The terminal ileum is transected obliquely

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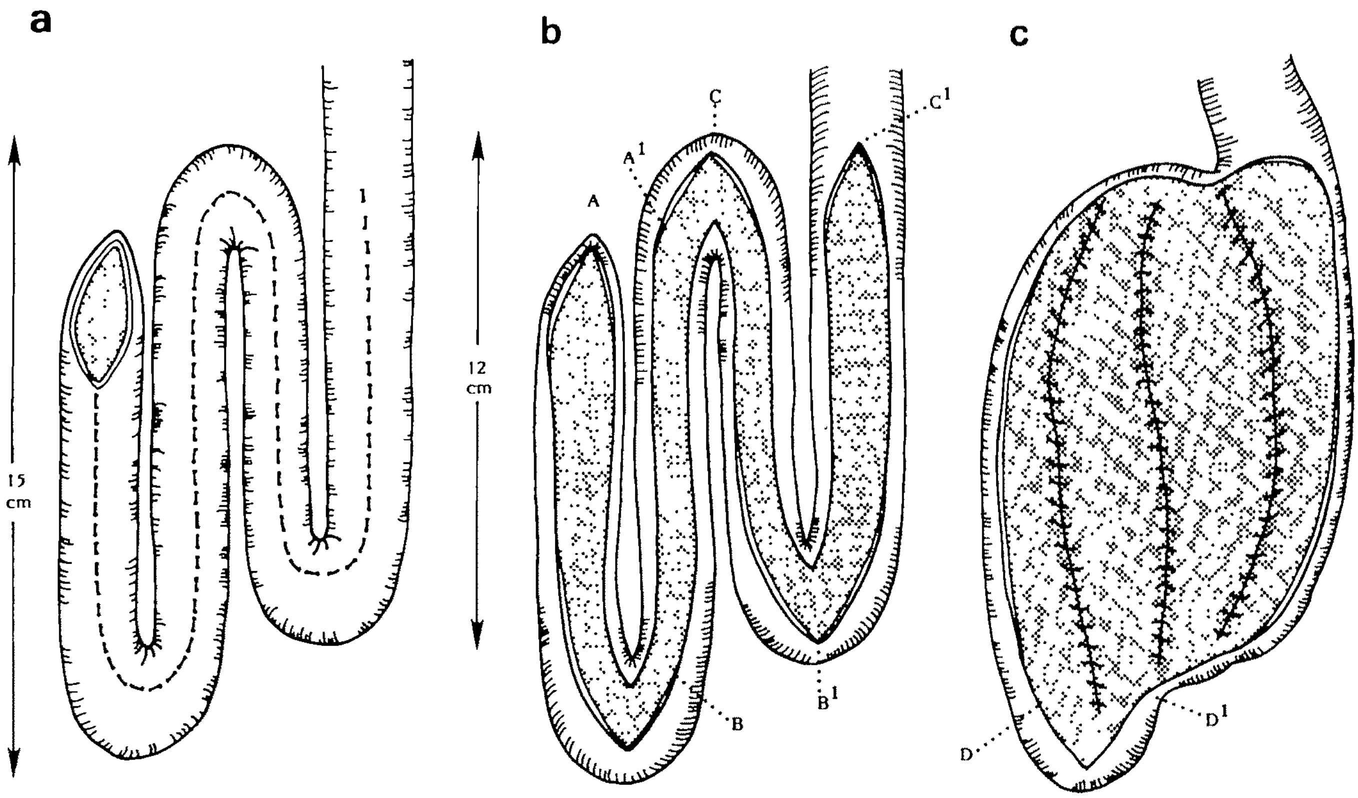

Figure 1 a *The terminal ileum laid out with the cut distal end on the patient's right showing the line of incision on the antimesenteric border of the bowel,* b *the bowel after it has been opened: A is joined to A^1, B to B^1 and C to C^1,* c *the three completed posterior suture lines: D is joined to D^1*

just proximal to the ileocaecal junction and the specimen removed. At this stage the vessels of the small bowel mesentery are inspected. The terminal ileum must come down into the pelvis without tension and, to obtain increased length, the ileocolic artery and, if necessary, some of the arcade vessels of the superior mesenteric artery are divided. The base of the mesentery may also require mobilization by dissection of the main vascular pedicle off the posterior abdominal wall and duodenum When fully mobilized the terminal ileum should extend several centimetres below the symphysis pubis.

Mucosal proctectomy A Parks' retractor is inserted into the anus and the submucosa injected with 1/300000 adrenaline solution. The mucosa is divided just above the dentate line and, with scissors, dissected off the underlying muscularis propria in four strips. Care is taken not to damage the muscle in stripping the mucosa or by excessive use of diathermy

Construction of the reservoir (Figures 1–3) The terminal ileum is laid out as four loops with the obliquely cut distal end lying on the patient's right (*Figure 1a*) Each of the four limbs, which measure approximately 12, 12, 15 and 12 cm in length (from proximal to distal), is held with Babcock forceps A seromuscular stay suture is inserted at the inner aspect of each of the three bends and these are used at the completion of the reservoir to inspect the posterior suture lines The bowel is then incised along the antimesenteric border (*Figure 1b*) and the cut edges approximated with a continuous all-layer suture of 3/0 Polyglyconate (Maxon®, Davis and Geck, UK) The stitching of the three posterior suture lines is done from the mucosal surface of the bowel (*Figure 1c*). The outlet of the reservoir is then constructed by approximating the inferior portions of the posterior wall (*Figure 2*). This needs to be sufficiently large to admit the blades of the Parks' retractor when the ileoanal anastomosis is performed and should normally admit two fingers. A mucosa burying stitch is used to construct the anterior suture line This begins inferiorly at the outlet of the reservoir and is continued proximally to the inlet, which should have a wide oblique opening. The suture line is carefully inspected The points where two suture lines meet are reinforced as are any places where there is a gap between stitches The capacity of the reservoir is then measured, using a bladder syringe, and its watertightness is tested The capacity usually ranges from 150 to 300 ml Two lateral stay sutures are placed at the outlet of the reservoir to guide it into the pelvis

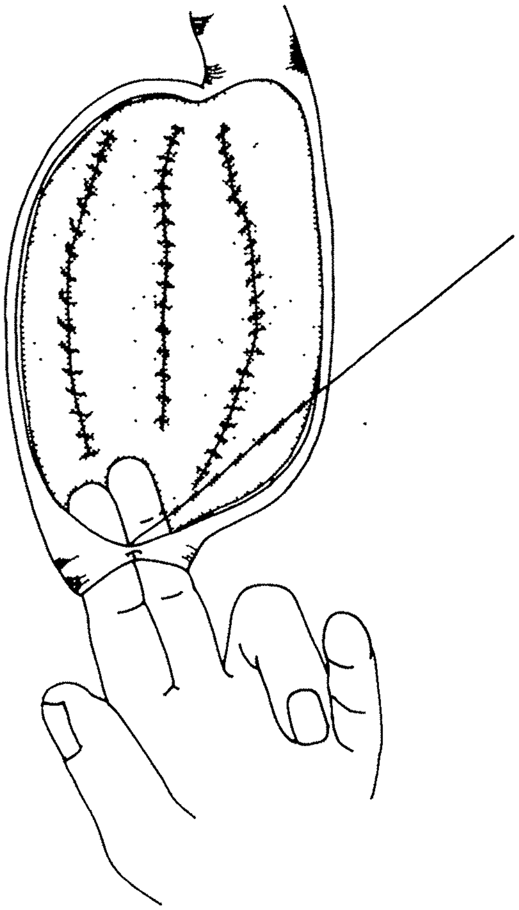

Figure 2 *Construction of the outlet of the reservoir which should admit two fingers*

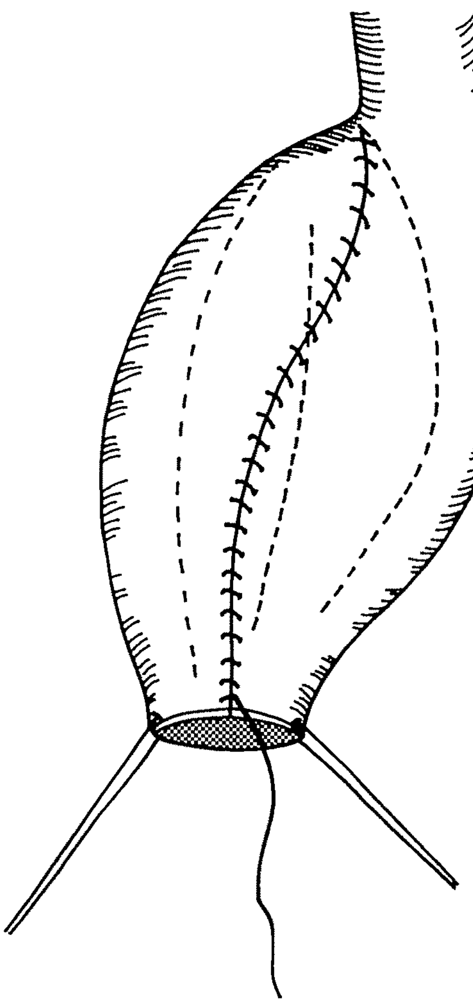

Figure 3 *The completed reservoir showing the anterior suture line with the anterior suture line stitch left long to orientate the pouch, and two lateral stay sutures to guide the reservoir into the pelvis*

(*Figure 3*) and the cut end of the anterior suture is left long to aid in its orientation.

Ileoanal anastomosis A Parks' retractor is used with shortened blades which enables the reservoir to be passed through the opened blades into the anal canal by applying traction on the lateral stay sutures. The anterior suture line stitch of the reservoir is then picked up with a haemostat. The ileoanal anastomosis is constructed with interrupted stitches using 2/0 polyglactin (Vicryl®), on a J needle (Ethicon Ltd., UK) which can be readily manipulated in a confined space. A stitch is first placed on either side of the anterior suture of the reservoir and one stitch is placed posteriorly. The Parks' retractor is then removed and holding the lateral stay sutures the blades are reinserted into the pouch. A stitch is placed at 90° and 270° and then each quadrant sutured in turn with another three or four stitches With each stitch the needle first picks up the free edge of the opening of the reservoir and then a small bite of the internal sphincter half way up the anal canal emerging at the cut edge of the mucosa. When the stitches are tied the suture line is pulled upwards and comes to lie in the midanal canal Care is taken not to take deep bites of the anal canal anteriorly where, in women, a fistula between the reservoir or anal canal and the vagina may result. Two Redivac® (O.E.C Orthopaedic) drains are passed between the posterior aspect of the reservoir and the anal canal and brought out through the abdominal wall. Finally a Medina® (Astra Meditec, UK) catheter is guided into the reservoir by the abdominal operator and sutured to the buttock with a nylon stitch

A temporary defunctioning loop ileostomy was fashioned in 40 patients, in the remaining 20 this was omitted

Postoperative management Gentamicin 80 mg and metronidazole 500 mg IV are given at the start of the operation and continued 8-hourly for 4 days. The Medina catheter is removed on the 5th or 6th day, or earlier if it becomes blocked, and the urinary catheter removed at the same time.

Patients who have had a defunctioning ileostomy performed are reviewed in the outpatient department at 1 month Digital examination, sigmoidoscopy and X-ray examination of the reservoir are carried out and if these are satisfactory the ileostomy closed

Follow-up. Patients were seen regularly at 3–6-month intervals by the author The mean follow-up was 29·6 months In addition all patients completed a detailed questionnaire.

Results

Complications

There were no perioperative deaths. One patient died of amyloid disease 7 years after surgery but this was present at the time of operation.

The postoperative complications following restorative proctocolectomy are shown in *Table 1*. The late complications are shown in *Table 2*.

The most significant postoperative complication was sepsis, occurring in 18 per cent of patients. A further six patients developed late perineal infection bringing the total incidence up to 28 per cent. Septic complications occurred mainly early in the series. Comparing the first 30 cases with the second 30 cases, the postoperative sepsis rate fell from 20 to 4 per cent and the total sepsis rate from 37 to 23 per cent. In five cases surgical intervention was necessary to deal with these complications.

Intestinal obstruction was also common (overall incidence 18 per cent). It occurred six times in the immediate postoperative period and all resolved spontaneously. Laparotomy was required in four of five late obstructions.

Reservoir ileitis was equally common (20 per cent). The diagnosis was made mainly on sigmoidoscopic appearance and

Table 1 *Postoperative complications in 60 patients following restorative proctocolectomy*

Complication		Outcome
Sepsis	11 (18)	
Anorectal suture-line leak	3	
Major leakage	1	Removal of pouch
Minor	2	Temporary ileostomy Anovaginal fistula
Reservoir leak	2	
Peritonitis	1	Drainage and temporary ileostomy
Fistula with abdominal wall	1*	Healed
Peritoneal infection	4	
Contamination	1	Laparotomy and drainage
Parastomal abscess	1	Discharge
Minor	2†	Settled with antibiotics
Wound	3	
Obstruction	6 (10)	All resolved
Pulmonary embolus	1	
Toxic psychosis	1	
Electrolyte disturbance	1	

Values in parentheses are percentages. * Also had wound infection; † demonstrated on indium-labelled leucocyte scanning

Table 2 *Late complications*

Perineal sepsis	6 (10)
Ischiorectal abscess causing fistula	2
Perianal abscess	1
Pouch–vaginal fistula	1
Anovaginal fistula (Crohn's 1)	2
Obstruction	5 (8)*
Anastomotic stricture	3 (5)
'Pouchitis'	12 (20)
Haemorrhage from pouch (amyloid disease)	1

Values in parentheses are percentages. * Four required laparotomy

Table 3 *Hospital stay for one- and two-stage procedures*

	No of patients	Hospital stay (days)	
		Total	Mean
Two-stage			
First stage	37	663	17·9
Second stage	37	368	9·9
Total	37	1031	27·9
One-stage			
Uncomplicated	16	188	11·7
Complicated	4	169	42·2
Total	20	357	17·8

confirmed by biopsy in most cases. In one instance, the symptoms were sufficiently bad to necessitate removal of the reservoir. Four additional patients required hospital admission to treat diarrhoea and electrolyte imbalance, whilst in eight the symptoms were less severe. Metronidazole or Augmentin (Beecham, UK) controlled symptoms in all but one case but many patients remained on a small dose of antibiotics for several months.

Stricturing of the ileoanal anastomosis occurred in three patients (5 per cent). In two cases this was minor. In one case, this was more severe and resulted from pelvic sepsis. All responded to digital dilatation.

In four cases (7 per cent) it was necessary to remove the reservoir and re-establish a permanent ileostomy. In two patients this was due to technical failure occurring early in the series: one as a result of anastomotic dehiscence and one from recurring 'pouchitis' due to impaired emptying. In the other two cases the reservoir was removed after some years: one because of Crohn's disease and the other because of bleeding from amyloid disease.

The most objective assessment of the incidence and severity of postoperative complications is by measurement of hospital stay. Comparison of the first 25 with the last 25 cases showed a highly significant difference in hospital stay between the two groups (mean 31·8 days, range 12–124, s.d. 26·0 compared with a mean of 15·6 days, range 8–34, s.d. 7·0; $t = 2·977$, d.f. 48: $P < 0·005$). Three serious complications occurring early in the series were largely responsible for this difference.

Although the majority of patients ($n = 40$) had a defunctioning ileostomy and therefore underwent a two-stage procedure, 20 patients had a single-stage procedure without ileostomy (15 for ulcerative colitis, five for familial adenomatous polyposis). The length of hospital stay in 37 patients in whom the ileostomy had been closed was compared with that in the 20 patients who underwent restorative proctocolectomy without an ileostomy. The results of the two groups are given in *Table 3*. Four patients in the single-stage group developed complications and in two this necessitated establishing an ileostomy. The majority however did well and overall a significant reduction in hospital stay was achieved by a one-stage procedure.

Function

Only one patient with an S reservoir had to use a catheter for evacuation. One patient with a W reservoir preferred to use a catheter intermittently to relieve tenesmus although he can evacuate normally.

The functional results for 48 W reservoirs are given in *Table 4*. These results do not differ significantly from the series as a whole except that one patient with an S reservoir was incontinent.

Of the patients that had to evacuate at night only one-third found it necessary to take antidiarrhoeal agents. Minor impairment of continence resulted in occasional soiling or a mucous leak at night but not sufficient to cause soreness or necessitate wearing a pad.

Sexual function was normal in all 29 men who were questioned and there were no cases of impotence or retrograde ejaculation. Two of the women became pregnant and had normal vaginal deliveries.

Patients were asked to assess the result of their operation as excellent, good, satisfactory or bad and the conclusions are given in *Table 5*. There were two failures occurring early in the series where the reservoir had to be removed. Two further patients who had satisfactory results at the time of completing the questionnaire subsequently went on to have their reservoirs removed, one because of Crohn's disease and the other because of bleeding from amyloid disease. Ninety-eight per cent of patients with W reservoirs and 96 per cent of the series as a whole were well satisfied with the result of their surgery.

Discussion

Restorative proctocolectomy is a relatively safe procedure with low operative mortality. In 596 patients collected from various sources the mortality rate was only 0·3 per cent[10]. The morbidity was however considerable. There are two major postoperative complications: sepsis and intestinal obstruction.

A high incidence of infective complications has been reported by most authors, but this decreases with experience. This was certainly the case in this series where the postoperative sepsis rate fell from 20 to 4 per cent. Pelvic sepsis is the major problem[10] and is often the result of dehiscence of the ileoanal suture line. Sepsis can be prevented by avoiding contamination by washing out the rectum before its division, avoiding pelvic haematoma by meticulous haemostasis when the rectum is divided and by accurate suturing of the ileoanal anastomosis. The latter is the most difficult part of the operation but is greatly facilitated by placing the blades of the Parks' retractor within the pouch and the use of an atraumatic suture on a J needle.

The length of the anorectum that is left seems to be of little importance from a functional point of view[7] and there appears to be no harm in dividing the bowel as low as the anorectal junction. Division of the rectum too high simply makes the procedure more difficult. The removal of the additional mucosa may result in haematoma and the cuff of rectum may obstruct the pouch being brought down into the anal canal.

In the construction of the reservoir there are two ideals. Firstly, catheterization of the pouch should not be necessary

Table 4 *Functional results in 48 W reservoirs*

Catheter evacuation	0	
Evacuations per 24 h*	3·8 ± 0·2	
UC	4·1 ± 0·2	$t = 3·53$†, d.f. 46, $P < 0·001$
FAP	2·6 ± 0·3	
Evacuation at night		
Not at all or rarely	31 (65)	
Up to once a night	17 (35)	
More than once	0	
Antidiarrhoeal drugs	21 (44)	
Continence		
Normal	24 (50)	
Minor leakage	22 (46)	
Frequent leakage (pad)	2 (4)	
Incontinent	0	

Values in parentheses are percentages. * Mean ± s.d., † statistical analyses were by unpaired *t* test. The mean follow-up was 23 months, none was followed up for less than 6 months

Table 5 *Patients' assessments of results*

	All cases ($n = 55$)	W reservoirs ($n = 48$)
Excellent	43 (75)	38 (79)
Good	8 (14)	7 (15)
Satisfactory	2 (4)	2 (4)
Bad	0	0
Failures	2 (4)	1 (2)

Values in parentheses are percentages

and secondly the number of evacuations should be reduced to a minimum. The fact that catheterization was necessary in almost 50 per cent of S pouches was shown to be due to the long distal ileal segment[6] and, if this was shortened, Dozois *et al.*[7] felt that the problem could be eliminated. Even if this is the case, the S pouch suffers from the disadvantage that the opening can only be made as wide as the ileum. For accurate ileoanal anastomosis the author believes it is essential to place the blades of the Parks' retractor within the reservoir; in some instances the terminal ileum is too narrow for this to be possible. The surgeon therefore has the choice of a J or W reservoir. Nicholls[3] believes that the frequency of evacuation is inversely related to the capacity of the reservoir. He found that J pouches had a mean capacity of only 172 ml whereas W pouches had a mean of 325 ml. The corresponding frequency of evacuation was 5·5 and 4·1 per 24 h respectively. In a larger series Nicholls and Lubowski[9] report a frequency of 3·3 which compares favourably with 3·8 in this series. It can be argued that it should be possible to construct a J reservoir of equal capacity by making the two limbs sufficiently long. However no one has so far reported a series of J pouches where the mean frequency of evacuation has been less than 5 times per 24 hours.

The construction of a W pouch is no more difficult than a J pouch The ideal capacity for a reservoir has not yet been determined but it would be relatively easy to increase this. A very large reservoir may however fail to empty adequately The capacitance, or ability of the reservoir to stretch, may also be of importance and this could be less with a double-layer suture technique The author has used a single layer of continuous 3/0 polyglyconate. This has been satisfactory in every instance where a defunctioning ileostomy has been performed, and barium examination has failed to show any leakage. In two cases, however, leakage occurred from reservoirs that had not been defunctioned. A single-layer technique therefore may not be ideal.

The avoidance of a defunctioning ileostomy is controversial. It should certainly be performed in every case until the surgeon is confident about performing the ileoanal anastomosis. If this is entirely satisfactory without tension, with a good blood supply, accurate suturing and the patient not on high dose steroids, then it is probably safe to omit an ileostomy. It would probably be safest, however, to drain the reservoir with a Medina catheter for 7 days postoperatively because the strength of anastomoses is very small up until this time[12].

Avoiding an ileostomy has obvious attractions in decreasing the number of operative procedures and the hospital stay. Loop ileostomies are often difficult to manage and may result in additional admissions because of ileostomy diarrhoea, skin excoriation or obstructive episodes.

The overall results of restorative proctocolectomy compare favourably with those of proctocolectomy and ileostomy The subjective assessment shows that 95 per cent are well satisfied with the procedure Frequency of evacuation is usually well tolerated because of the absence of urgency and the fact that the patient can delay defaecation until it is convenient. Night evacuation is a minor problem with the W pouch[9]. Although Nicholls and Lubowski found that in 92 per cent of their patients continence was normal, this was not the case in this series. In almost one-half of the patients there was a minor impairment of continence resulting in occasional leakage on exertion or a mucous leak at night. This, however, was of little inconvenience to the patient and neither necessitated wearing a pad, nor taking antidiarrhoeal drugs. The difference in the results of the two series is probably related to the method of assessment Nicholls and Lubowski[9] give figures for 'normal' continence and faecal leakage but it seems likely that there is a group between these two where continence is not entirely normal

In this series a simple preoperative assessment of sphincter tone was made by digital examination, and physiological tests of sphincter function were not performed In the two patients that had frequent leakage following surgery, one appeared to develop sphincter impairment after a protracted illness, the other had good sphincter tone with severe reservoir ileitis. Preoperative tests of sphincter function might have identified the former but on the whole it was felt that they would have contributed little.

The preservation of normal sexual function is of the utmost importance in treating such a young age group and it is encouraging that there have been few reports of impotence following restorative proctocolectomy. It is, however, disturbing that Dozois[11] reports a 9 per cent incidence of retrograde ejaculation owing to damage of the hypogastric nerves. Nicholls and Lubowski[9], who make a point of keeping the plane of dissection close to the rectum, have had no cases of retrograde ejaculation. Damage to the hypogastric nerves may occur in the lumbosacral region and it may be equally important to lift the mesorectum off the posterior abdominal wall at this point where the hypogastric nerves should be clearly seen and traced into the pelvis. The author has had no instances of retrograde ejaculation in 29 men he has operated on and believes that visualization of these nerves is as important to their preservation as it is, for example, in avoiding damage to the recurrent laryngeal nerves at thyroidectomy. The most significant problem in the long term has been reservoir ileitis which in this series has occurred at some stage in 27 per cent of patients, and often required long term antibiotics. Further research into the aetiology and treatment of this condition is required.

The incidence of complications following restorative proctocolectomy and ileal reservoir, when performed by surgeons who have gained experience of the procedure, is acceptable In the opinion of the author, this operation is the procedure of choice and should be offered to the majority of young people with ulcerative colitis or familial adenomatous polyposis. However, it is recommended that the operation should be performed in a few centres where surgeons can gain sufficient experience to obtain good results.

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Computer-aided diagnosis: a review

G. C. Sutton

Pontefract Health Authority,
Ackton Hospital, Pontefract
WF7 6HT, UK
Correspondence to:
Dr G. C. Sutton

Fifteen years ago, computer-aided diagnosis of the acute abdomen promised much. Today it is little used. Studies have been flawed by poor trial design, bias, selective reporting of results, statistical naivety and spurious conclusions. The computer system lacks 'common sense' and is less accurate than clinicians. Yet its introduction has been associated with improved patient management and outcome. Much of the effect arises from structured data collection methods and some from audit feedback to clinicians. It is on these innovations, not on the computer, that future work should focus.

Keywords: Computer-assisted diagnosis, acute abdomen

In 1972, de Dombal and co-workers in Leeds described a system for computer-aided diagnosis of the acute abdomen. Results[1,2] were spectacular: the computer had a diagnostic accuracy exceeding that of a consultant surgeon, and there were improved rates for negative laparotomy and perforated appendix. Over 15 years on, computers are common in the National Health Service, UK, yet their impact on clinical decision making is muted. Whatever happened to this promising development?

The literature of computer-aided diagnosis is extensive but much is theoretical or speculative, the present review considers only the practical effectiveness of computer-aided diagnosis and is restricted to published scientific accounts. It focuses on the acute abdomen as this is a clinically important, well-documented test area for computer diagnosis There are relatively few diseases to consider. Correct diagnosis should lead promptly to correct management decisions and improved patient outcome; unaided human performance is far from satisfactory Definitive diagnoses may be swiftly established. It is a uniquely clear-cut decision making domain, so if the technique is not of demonstrable benefit here its credibility in other clinical fields must be undermined

Systems for computer-aided diagnosis have three components Firstly, doctors record the relevant details (the indicants) on structured record sheets. For the acute abdomen these are symptoms and signs, but results of investigations can be handled in the same way. Secondly, these indicants are keyed into the computer, often (at least in trials) by some other person. The computer compares the present findings with a database and uses a statistical formula to calculate the diagnosis. Usually this is withheld until clinicians have made their own decision. The third component is some form of feedback. The relative contribution of forms, computers and feedback is immaterial to the pragmatic effect of the total 'package', but it is critical to explanations and policy decisions derived from trials

Key aspects of trial methodology are thus the structured data form, the formula for calculating the diagnosis, the database, the interaction with the computer, the audit feedback, the setting and design of the trial, and the presentation and interpretation of results.

Structured data forms

The quality of hospital records (especially casualty records) is uneven; important data are ambiguous, illegible or omitted Structured data collection constitutes a major change and may account for most benefits claimed for computer-aided diagnosis Note that baseline accuracy figures are culled from ordinary case notes, in which junior doctors often fail to record diagnoses. If these are marked 'wrong', accuracy will appear to rise when structured methods enforce this discipline In the UK multicentre study[3], clinical accuracy rose from 45·7 to 56·7 per cent with the use of forms alone, and to 65 per cent or more when computers or feedback were added. Similar rises were seen in Scottish[4] and Scandinavian[5,6] studies with no computer on site, the forms being sent to Leeds for analysis. Computer diagnosis and feedback would have been so long delayed that only the use of structured forms is likely to have affected results.

Calculating the diagnosis

Diagnoses have been calculated by Bayes' formula, other statistical methods such as discriminant functions, and artificial intelligence. Such methods calculate the likeliest diagnosis and do not deal in certainties. In contrast, the sort of classical (binary, Boolean or algorithmic) logic traditionally used by computers makes exact deductions ('If symptoms are A plus B then the disease is D') and has little relevance to clinical practice.

Most workers have used Bayes' formula, the modern version of which derives from probability theory and differs considerably from its 18th century ancestor. It assumes that:

(a) The patient has one (and only one) of the diseases known to the computer. (Yet there will always be patients with other diseases and multiple pathology is not uncommon. The surgeon can mentally set aside the dyspepsia or dysmenorrhoea to consider what symptoms remain unaccounted for by that background; Bayes' formula cannot.)

(b) Indicants are independent. (Yet many are highly correlated, such as 'site of pain at onset' with 'site of pain now'. Thus the computer either counts the same pain twice or misses the special significance of shifting pain.)

(c) The probabilities of all relevant diseases and indicants are known with sufficient precision. (See section on 'Database')

Bayes' formula contains a term $P(D_k)$ for disease frequency which many systems omit. This causes over-diagnosis of uncommon conditions; computer diagnosis of Crohn's disease[7] failed partly for this reason.

Discriminant functions have been used for the diagnosis of dyspepsia[8] and appendicitis[9] Each indicant is assigned a weighting factor. Then adding up the relevant indicants (weighing the clinical evidence, as it were) generates a figure x; if this exceeds a pre-set threshold the disease in question has been diagnosed Multiple pathology can be diagnosed by this method.

The promise of artificial intelligence remains unfulfilled. Systems using rule-based inference and 'fuzzy logic' have been tested on antibiotic therapy[10] and general internal medicine[11]. Their diagnoses were often catastrophically wrong and, therefore, their performance was unsafe.

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Methods have seldom been compared by matched trials. In 300 patients with upper gastrointestinal complaints, Bayes' and discriminant analysis were equally accurate[12], but only 11 symptoms were considered. Bayes' and rule-based inference had equal accuracy in 50 cases of dyspepsia[13]. In a trial of ten methods on 1991 cases of liver disease, Bayes' narrowly won[14].

No method is satisfactory. Bayes' is the best documented and no alternative has beaten it, at least for gastrointestinal disease. One would therefore expect any proponent of a new method to have made a matched comparison. Poor diagnostic methods limit the accuracy of the computer but do not invalidate trial results

Database

Key questions in assessing a database are the range of diseases covered, the indicants and the methods used to compile it.

Databases for the acute abdomen usually cover appendicitis, diverticulitis, perforated peptic ulcer, non-specific abdominal pain, cholecystitis, bowel obstruction and pancreatitis[15]. Renal colic and dyspepsia are added by some. The Leeds (UK) database for lower abdominal pain in women[16] covered ectopic pregnancy, ovarian cyst, appendicitis, incomplete abortion, pelvic inflammatory disease, urinary tract infection and non-specific pain.

The Leeds dyspepsia database covered chronic cholecystitis, duodenal ulcer, gastric ulcer, gastric cancer and functional (i.e., non-specific) dyspepsia; curiously, oesophageal conditions were omitted[17]. It is surprising how rigidly separate databases have persisted, despite the advantages of integration.

The acute abdomen database organized indicants into 33 groups with 135 possible replies[15]. Pulse and temperature, which are traditionally taught as informative signs, were notable omissions. 'History' was categorized as 'previous surgery' or 'no previous surgery' as if it were irrelevant whether the patient had had an appendicectomy, a hernia repair or a palliative operation for advanced malignancy. Likewise the categorization of 'drugs' as 'being taken/not been taken' was jejune There were no questions about past illness relevant to the present pain: known ulceration, Crohn's disease or gallstones. The criticism is not of the early workers' imperfect attempt, but the unthinking way in which similarly weak databases are still used.

The method of compiling the database will determine whether it can support valid diagnostic inferences. Critical points are the collection site, source record structure (or lack of it), the number of cases and the handling of 'zero' data. Generally data have been collected from hospital patients; they may not be valid for out-patients or cases seen at home by general practitioners. However geographical differences[18,19] do not appear important, at least within North America and Europe.

Early databases were collected from ordinary case notes, with all their omissions and ambiguities. Better data are obtained from structured records of consecutive, unselected patient series which trials of computer-aided diagnosis create as a spin-off. Such series have been collected for acute abdominal pain[18,19] but the list of indicants is still unrealistic.

The larger the series the more robust the data, though size does not overcome collection biases. More important than total size is the number of patients with each condition · 500 people with an acute abdomen might include only ten with pancreatitis. When thousands are available there may be benefits in subdividing some conditions. For instance the term 'non-specific abdominal pain' covers both constipation and gastroenteritis, so that the indicant 'bowel frequency', which is almost pathognomonic, becomes uninformative. If a certain indicant does not occur (e.g , no left loin pain in 100 cases of appendicitis) it cannot be set a probability of 0 per cent or its occurrence will absolutely rule out the disease. The value chosen should reflect confidence limits of the series Early databases contained many values of 0·1 per cent, which would have needed a sample size of 1000 to justify.

The early databases were flawed but creditable attempts; it is disappointing that later versions perpetuate many of their failings. Poor databases, like poor diagnostic methods, do not invalidate trial results but may limit the computer's accuracy.

Interaction with computer

Because Bayes' formula is so simple, and technology is progressing so rapidly, the computer hardware and software are largely irrelevant. More interesting is the doctor–machine interaction. Early computer systems were user-unfriendly, even within the limits of their technology, but modern equipment is outgrowing this problem. More seriously, systems offend clinical common sense. The example of drugs 'taken/not taken' has been mentioned, and similar absurdities abound. Systems generally request patient data in a rote sequence, deaf to the answers received. The sequence needs branches, to allow important detail to be pursued or superfluous questions to be skipped. Branches for dyspeptic or gynaecological symptoms, for instance, could merge the present separate databases.

In the UK multicentre study[3], doctors used the computer in 44·5 per cent of eligible cases, a further 29·6 per cent being entered by clerks. This overall figure conceals peaks and troughs; in Winchester it ranged from 64 per cent to below 10 per cent[20]. New junior doctors, it seems, start with enthusiasm but abandon the computer after a few months.

Thus, unfriendly systems may fail in three ways. Firstly, clinical data may be entered incorrectly. Secondly, such systems become disused and discredited. Thirdly, they may be anti-educational, for instance when recording previous surgery the doctor might put just 'yes' or 'no' in the case notes. It is not known whether these effects are significant.

The computer is only part of a package—yet it is the one item published papers highlight in their titles and in their concluding calls for more resources. But its specific contribution, over and above the effect of forms and feedback, remains ill-defined.

Audit feedback

Learning from experience should be part of routine practice. Feedback can take many forms, such as seeing the viscera at laparotomy, case discussions, or audit review of unit statistics. Units practise it to varying degree, and general practitioners and casualty doctors tend to miss out. One side-effect of a trial of any diagnostic technique—but not perhaps its service use—is to foster a comprehensive system of feedback and postgraduate education.

Few accounts of computer-aided diagnosis show in detail how and when feedback was given. It would be disastrous, for example, if a computerized score sheet of doctors' accuracy was seen as a substitute for proper case review. In Leeds, both clinician and computer accuracy fell when feedback stopped, recovering when it was reinstated[21], but the change appears not to be statistically significant. In the UK multicentre trial[3], junior doctors' accuracy rose from 56·7 to 64·8 per cent when feedback was added to forms, and to 68 per cent when computers were used as well. Learning curves rose more quickly with computers and at Winchester accuracy correlated with usage[20]. Perhaps the most striking result is the flat learning curve during the baseline period and when using forms alone. In other words, junior doctors in those units were no better after 6 months' training than when they arrived. This is a serious indictment of current training arrangements.

Trial design

It has often been unclear from publications which hypothesis, if any, is being tested. Key questions are:

Is the introduction of computer-aided diagnosis associated with useful change in clinical performance or patient outcomes?

Is the effect causal and, if so, which components are responsible?

Given the imperfect, incomplete data available at the time a clinical decision is required, can the computer generate a useful diagnosis/management decision in its own right, or is it simply echoing the clinician's opinion?

Four people typically assess the patient with abdominal pain: the patient him/herself, the general practitioner, the casualty officer and surgeon. In theory the computer could assist any of them but the acid test is how it performs on consecutive unselected cases. This usually requires a prospective design, although if structured patient records are in use, retrospective series may suffice. Note that if the series includes database cases, computer accuracy may be inflated. Trials on patients with selected diagnoses[22,23] are uninformative regarding performance on unselected patient populations.

The first decision in assessing an abdominal pain is the patient's own, to seek medical help. Computers have not been applied to this but in Glasgow they were used to pre-interview patients with dyspepsia[24]; the effect on process and outcome was not described In the Leeds area, structured pre-interviews were conducted by a non-medical assistant. Using this information, the computer was 81 per cent accurate on selected cases with dyspepsia[25] or with positive endoscopy findings[26] but scored only 65 per cent overall. Systems have been produced for use by crew of long-range submarines and spacecraft[27], but the quality of patient information was poor and computer accuracy was not stated

Computer-aided diagnosis has not been tested in general practice. Hospital studies imply that general practitioners have low accuracy on cases referred for surgical opinions[1,28], but this ignores patients managed without referral[29,30]. Each year in a list of 2000 patients, some 200 consult the general practitioner for abdominal pain, but only ten are sent to hospital as emergencies. Computer assistance is unlikely to better this performance

Casualty staff are similarly disadvantaged by ward-based studies as cases discharged without admission, on which their accuracy is highest, are ignored. Casualty staff were 45 per cent accurate in the initial Leeds trial[1] but 65 per cent accurate in a casualty-based study[31], as was the computer. The change largely reflects the method of measurement.

The striking feature of hospital-based studies is how few have actually tested computer assistance to clinicians Doctors have generally filled in structured forms and handed them to assistants for entry; the computer's diagnosis has been withheld and feedback delayed Only forms are tested by such trials.

Some trials have given the computer 'multiple guesses': the computer runs once with a surgical database, once with a gynaecological database, and so on, and the answer nearest to the final diagnosis is chosen in retrospect. This inflated computer accuracy from 55 to 70 per cent in casualty[31], and from 62 7 to 68·2 per cent in the multicentre study[3] Another biased practice is to mark the computer right when it is 'as near as it can get', for instance if renal colic is not in the database and the computer picks urinary tract infection instead[16]. The 'computer diagnosis' is normally the condition awarded the highest probability but sometimes printouts such as 'cancer 12 per cent, gastric ulcer 88 per cent' are taken as diagnosing cancer[32]. This is only valid if the lower threshold was set in advance

The patient's final diagnosis is crucial to evaluation; methods for establishing it have seldom been given in detail. If the trial aims are explanatory, diagnoses may need to match an explicit list of criteria. In a pragmatic trial (the majority) this is unnecessary, but ideally some independent blind observer should adjudicate on equivocal pathology results. Otherwise improvements in, say, negative appendicectomy rates may merely reflect altered scoring habits.

Presentation and interpretation of results

The simplest measure of performance is the number of correct and incorrect (or total) diagnoses, but even this has not always been given. Some accounts have given figures for selected subgroups, with overall scores being studiously ignored. Publications should also include full 'discriminant matrices', i.e. computer and clinical diagnoses *versus* final diagnosis Accuracy may vary markedly between different conditions, as will the consequences of mistakes. The full matrix reveals the system's sensitivity, reliability, specificity and diagnostic power.

It is astonishing how seldom doctors and computers have been directly compared on the same patient on the same occasion using the same indicants. Even when they have been compared, only summary data have been given; information on matching is lost and appropriate statistical tests (e.g. McNemar's test for paired binary data) cannot be applied In fact there has been a glaring lack of statistics, such as standard errors of accuracy rates, so that the significance of many results is unproved.

From some accounts the reader can derive standard errors and apply unmatched tests, which are weak but conservative. Correcting for biases of the types described earlier (where these can be quantified), the computer was significantly more accurate than clinicians in the initial Leeds trial[1,2], in gynaecological complaints[16], on X-ray appearances in Melbourne, Australia[8] and on right iliac fossa pain in Georgia, USA[33] Clinicians and computers were about equal in Sheffield (UK) children[34], whereas clinicians did better in Denmark[35], in casualty[31] and (marginally) in the UK multicentre study[3].

Computer and clinical accuracy have averaged about 65 per cent, a more realistic level than the early computer scores of 90 per cent. Even when the computer is more accurate than clinicians it is less safe, although it may be associated with improved clinical safety. In the UK multicentre trial clinicians' 'bad decision' rate fell from 6·3 to 2·7 per cent and their 'bad management' rate from 0·9 to 0·2 per cent.

Measures of performance or outcome include the proportion of patients sent home from casualty without admission, negative laparotomy rate, perforated/gangrenous appendix rate, and savings in bed nights or monetary costs. As with accuracy, results are often missing or selective. Thus the rates for perforated, gangrenous or normal appendix reported from Leeds[1] referred to the best batches; overall rates were not significantly better than post-trial figures. The Scottish study (effectively forms-only) saw major 'improvements'[4]; confusingly, baseline figures did not tally with those for the same hospital in a companion paper[28]. Yet if the effects described are real they are large enough to be of practical benefit. There is also a persuasive trend in the figures, suggesting a learning curve. The criticism is that trials have not been properly designed, either to quantify a desirable change or to determine its cause.

The best evidence to date comes from the UK multicentre study[3]. Computer-aided diagnosis was associated with improved negative laparotomy rates (from 313 to 174 a year), perforated appendix rates (from 23·7 to 11·5 per cent), shorter hospital stays (from 4 to 3 3 days for non-specific pain, 6·7 to 5·4 for appendicitis), and an estimated annual saving of 4258 bed nights. It is important to clarify the cause of these benefits, which occur 'downstream' of the computer system.

Annual National Health Service savings of between 20 million and 25 million pounds sterling have been extrapolated from these figures. Such claims are difficult to verify, especially as savings are marginal: only the patients who are least ill have their hospital stay averted or shortened, so that average costs mislead. Yet the benefits of computer-aided diagnosis still appear to out-weigh its costs, for instance operations are not avoided by missing serious conditions. So the question is which components merit further investment of time, money and effort On a rough economic analysis, structured forms are low cost, high gain, and the case for their introduction is strong. Computers are high cost, low gain, and the case for introduction is unconvincing; feedback is low cost, low gain, the case for introduction is borderline and merits further research.

Discussion

Clinical decision making for the acute abdomen is unsatisfactory, the rationale for computer assistance remains strong and initial results were spectacular. Yet today it is little used. Too often its introduction has been associated with poor trial design, bias, selective reporting of results, statistical naivety and spurious conclusions. One suspects that investigators who were dazzled by the prospect of 90 per cent computer accuracy, were disillusioned when they could not replicate this and lost sight of the practical benefits Those benefits have been exaggerated by biased methods, but neither this nor chance fully explains them

At least half the rise in clinical accuracy, and perhaps a similar proportion for outcome measures, stems from structured data forms alone. Statistical analysis suggested that feedback played a lesser role than computers[3], but the feedback in question comprised computerized score sheets not systematic case review. Outcomes and all but the initial diagnostic score are 'downstream' of both structured forms and computers, and it is difficult to see what is contributed by computer diagnosis *per se*. Its accuracy is inevitably limited by that of the clinician providing the input. In no way do current systems act as experts in their own right, and they are unlikely to do so until they possess the 'deep knowledge' of basic medical science that underlies the simplest surgical diagnosis. They appear merely to rehash the clinician's own opinion while losing overall accuracy.

The computer's accuracy may matter less than its credibility. For instance, it is heavily influenced by peritoneal and right iliac fossa signs. A disagreement over 'query appendix' might make the doctor ask 'Do I really think this patient is guarding?' and thus ponder the elicitation and interpretation of that sign. But this effect will be swiftly lost once the computer's dangerous inaccuracy is seen. Perhaps the computer's true role then is in undergraduate education, but this needs separate testing and there may be simpler roads to the same end.

The likeliest cause of the outcome effects is the system of case review which research into computer-aided diagnosis (but not necessarily its service use) enforces. It stimulates postgraduate teaching, introduces surgical audit in a non-threatening way, and highlights organizational problems such as delays in taking appendicitis cases to theatre and poor record keeping. It is these areas, plus the use of structured forms, which should be the focus of future studies. Basic research into better diagnostic methods must also continue, and the acute abdomen remains its natural test field. Meanwhile, computer-aided diagnosis is in no fit state to be widely implemented in the National Health Service.

In an ideal world one would not need the glamour of computers to attract professional interest and research funds to improving management of the acute abdomen. If, in our real world, computers are so needed as a 'loss-leader' then they have had some value. Yet over the last 15 years they have consistently diverted attention from important, solvable issues, and further investment in them is likely to show minimal or negative returns. If the Department of Health, UK now wishes to ensure that all the money and professional time devoted to this field is at last translated into real gains, it should consider a different strategy. It should monitor performance indicators for the acute abdomen, and require districts falling below target to introduce structured records.

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A prospective randomized trial of Angelchik prosthesis versus Nissen fundoplication

R. C. Stuart, K. Dawson, P. Keeling, P. J. Byrne, and T. P. J. Hennessy

Department of Surgery,
St James's Hospital, Dublin 8,
Ireland

Correspondence to:
Professor T. P. J. Hennessy

A total of 61 patients with gastro-oesophageal reflux, resistant to medical therapy, were entered into a prospective randomized trial comparing the Angelchik antireflux prosthesis with Nissen's fundoplication. Both groups had a similar age and sex distribution and their reflux profiles were comparable. An Angelchik prosthesis was inserted in 30 patients and 31 underwent fundoplication. The mean duration of postoperative follow-up was 38 months. At clinical assessment 23 (77 per cent) of the Angelchik group were graded Visick grade I or II, compared with 29 (94 per cent) of the Nissen group. Assessment by 24 h pH monitoring and manometry between 3 and 6 months after operation showed that both procedures were equally effective in reducing reflux and increasing lower oesophageal sphincter pressure. However, long-term endoscopic follow-up revealed grade III oesophagitis in seven patients in the Angelchik group. No patient in the fundoplication group had grade III oesophagitis. Three of eight patients with strictures in the Angelchik group reported persistent dysphagia. All seven patients with strictures in the Nissen group were relieved of their dysphagia. Migration or erosion of the prosthesis did not occur. Three prostheses (10 per cent) were removed, two for dysphagia and one because of sepsis.

Keywords: Angelchik antireflux prosthesis, gastro-oesophageal reflux, Nissen's fundoplication, 24 h pH monitoring, oesophagitis

Controlled trials assessing the relative merits of antireflux procedures are rare[1–3]. Since Angelchik and Cohen first reported the results of their new surgical procedure for gastro-oesophageal reflux more than 25 000 Heyer–Schulte prostheses have been inserted[4] Although numerous subsequent reports have acknowledged the efficacy of the device in controlling reflux[5–7], only two groups reported the results of controlled clinical trials[2,3]. The uncontrolled nature of the majority of studies led to the adoption of extreme views, with the ease of insertion and the satisfactory results emphasized by some, while others stressed the alarming nature of the complications. In 1984 Bombeck pointed out that after the implantation of 14 500 prostheses 150 complications had been reported to the manufacturers[8]. He also pointed out that despite the spectacular nature of these complications the mortality rate was very low and that even if the complication rate was several times higher than that reported it was still a low complication rate relative to the number of prostheses inserted. Many of these complications were due to prosthesis migration, arising from a design fault which led to the tapes becoming detached The design of the prosthesis was improved by attaching the tapes circumferentially and between January 1982 and May 1985, 16 757 new-model Angelchik prostheses were used with only 6 (0·036 per cent) reported complaints[9]. Benjamin *et al* reviewed the complications of antireflux surgery and reported that the mortality and morbidity rates after insertion of the prosthesis were 0–<1 per cent, and 0–3 per cent, respectively[10]. These figures compare favourably with the reported mortality and morbidity figures for standard antireflux surgery, 0–4 per cent and 5–46 per cent, respectively[11–13].

Currently the most frequently used antireflux procedures are Nissen fundoplication, the Belsey Mark IV procedure, and Hill's posterior gastropexy. Comparative studies suggest that, of the three, fundoplication is the most satisfactory[1,14] but others have been less satisfied with the results of this operation[15]. It is evident that in order to evaluate the place of the Angelchik prosthesis in antireflux surgery the results of long-term controlled trials are needed. This paper reports our experience with the Angelchik prosthesis in a prospective controlled trial of the prosthesis *versus* Nissen fundoplication, with a mean follow-up of 38 months.

Patients and methods

Patients were admitted to the trial who had persistent symptoms of gastro-oesophageal reflux unresponsive to medical treatment Diagnosis was confirmed at endoscopy in all cases and supported by 24 h pH monitoring in the majority of cases. Manometry was performed where indicated to exclude motility disorders Oesophageal manometry was performed using a four-lumen polyvinyl catheter assembly with the four side holes spaced 5 cm apart from the distal end of the catheter and located 90° radially to one another The catheter assembly was perfused with a pneumohydraulic low compliance perfusion system and intraluminal pressure was transmitted via external transducers and recorded on a Devices* multichannel pen recorder The catheter assembly was introduced *per nares* in the fasting patient, passed into the stomach and withdrawn using a station pull-through technique until the high pressure zone was located at the distal oesophagus The lower oesophageal sphincter pressure was recorded as the difference between end-expiratory intragastric pressure and the maximal sphincter pressure at the respiratory reversal point. The sphincter pressure taken was the mean of 12 measurements performed on 3 pull-throughs.

After identification of the high pressure zone on manometry, the catheter assembly was withdrawn and an antimony-tipped pH electrode (Synectics Medical AB, Stockholm, Sweden) was positioned 5 cm above the high pressure zone Intra-oesophageal pH was recorded on a solid state Digitrapper (Synectics Medical AB) for a 24 h study period The 24 h pH data were stored and analysed on an IBM-PC computer using Synectics Esophagram version 5 09 software The data were analysed according to the total number of reflux episodes, total number of reflux episodes lasting longer than 5 min and the total time spent at pH 4 0 or less as a percentage of the study period

At laparotomy when the feasibility of both procedures was ascertained the patients were randomized by a closed envelope technique to undergo Nissen fundoplication or to receive an Angelchik prosthesis

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* *The Devices multichannel recorder is manufactured by Lectromed Ltd, Jersey, UK*

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All except one of the operations were carried out by the same surgeon (T.P.J.H.). Minimal dissection was used in placing the Angelchik prosthesis and after knotting the tapes the ends were secured with transfixion sutures rather than metal clips to avoid possible puncture of the prosthesis. When fundoplication was employed the aim was to provide a floppy wrap. The short gastric vessels were not routinely divided except when the spleen was high on the greater curvature. A 3 cm, 360° wrap was fashioned so as to admit easily a finger between the wrap and the oesophagus. Crural repair was carried out in both groups if the hiatus admitted more than three fingers. Three patients in the Angelchik group and two in the Nissen group underwent simultaneous cholecystectomy. One splenectomy was required in each group because of injury to the spleen. Patients with oesophageal strictures underwent dilatation at the time of surgery.

Postoperative follow-up was carried out by means of a questionnaire completed at outpatient review together with objective assessment by endoscopy, 24 h pH monitoring, and manometry.

A total of 61 patients were included in the trial. There were 30 patients in the Angelchik group and 31 in the fundoplication group. The mean age of patients in both groups was similar, being 50·1 years in the fundoplication group and 51·4 years in the Angelchik group. The male:female ratio in the fundoplication group was 18:13 and was 18:12 in the Angelchik group. The mean duration of symptoms was 4·7 years in the fundoplication group and 40·6 years in the Angelchik group. Both groups had similar pre-operative pH profiles (*Table 1*) and pre-operative manometric findings (*Table 2*). There were eight patients in the Angelchik group and seven in the fundoplication group with oesophageal strictures.

The mean duration of postoperative follow-up by means of questionnaire completed in the outpatients department (100 per cent response) was 38 months (range 18–56). Objective assessment by endoscopy, pH monitoring and manometry was performed at 3–6 months postoperatively. Further endoscopy was carried out for follow-up assessment of recurrent symptoms and therefore represents the current status of the patients.

Statistical evaluation of the differences in pH scores and sphincter pressures between the groups was by the Wilcoxon rank sum test for the analysis of non-parametric data. Evaluation of the differences in endoscopic and clinical grades was by χ^2, 2 × 2 contingency tables with Yates' correction.

Results

Clinical assessment

Of the patients in the Angelchik group, 23 (77 per cent) were either symptom free (Visick I) or had occasional mild symptoms which did not require treatment (Visick II); 29 (94 per cent) of the patients in the fundoplication group were graded Visick I or II. Of the seven (23 per cent) patients in the Angelchik group with poor results (Visick III or IV), severe and persistent dysphagia was present in three cases, and recurrent heartburn in five cases. One patient had both severe dysphagia and subsequent heartburn following oesophageal dilatation. In the two cases (6 per cent) in the fundoplication group with poor results (Visick III) this was due to recurrence of heartburn (*Table 3*). These differences did not reach statistical significance.

Oesophagoscopy

Postoperative oesophagoscopy was carried out in 25 of the patients in the Angelchik group and 24 patients in the fundoplication group. Of the 12 patients who refused postoperative endoscopy, 4 Angelchik patients and 6 fundoplication patients had a symptom status of Visick I, and 1 from each group was Visick grade II. Normal endoscopic findings were present in 16 patients in the Angelchik group and 19 patients in the fundoplication group. The remaining five patients in the fundoplication group had evidence of mild inflammation, whereas in the Angelchik group there were seven patients with moderate or severe oesophagitis and two patients with mild inflammation. These differences did not reach statistical significance.

24 h pH monitoring

Postoperative 24 h pH monitoring was carried out in 24 Angelchik patients and 21 fundoplication patients. Both groups showed a significant reduction in the severity of acid reflux

Table 1 *Pre- and postoperative 24 h pH profiles*

	Operative procedure		
	Angelchik prosthesis	Nissen fundoplication	*P* value (Angelchik *versus* Nissen)
No. of patients			
Pre-operative	20	18	
Postoperative	24	21	
Percentage time pH < 4			
Pre-operative	14·9 (2·4–41·6)	11·0 (1·0–53·6)	n.s.
Postoperative	1·1 (0–27·5)	0·6 (0–17)	n.s.
P value (pre- *versus* postoperative)	*P* < 0·05	*P* < 0·01	
No. of reflux episodes			
Pre-operative	42 (13–158)	48 (6–133)	n.s.
Postoperative	18 (0–76)	7 (0–94)	n.s.
P value (pre- *versus* postoperative)	n.s.	*P* < 0·01	
No. of reflux episodes > 5 min			
Pre-operative	9 (0–25)	5 (0–25)	n.s.
Postoperative	1 (0–13)	0 (0–7)	n.s.
P value (pre- *versus* postoperative)	n.s.	*P* < 0·01	

Median and range values are given. Statistical comparison is by the Wilcoxon rank sum test: n.s., not significant

Table 2 *Pre- and postoperative lower oesophageal sphincter pressures*

	Operative procedure		
	Angelchik prosthesis	Nissen fundoplication	*P* value (Angelchik *versus* Nissen)
Pre-operative pressure (mmHg)	13 (5–40)	12 (5–40)	n.s.
No. of patients	21	21	
Postoperative pressure (mmHg)	35 (15–70)	30 (12–45)	n.s.
No. of patients	22	19	
P value (pre- *versus* postoperative)	*P* < 0·05	*P* < 0·05	

Median and range values are given. Statistical comparison is by the Wilcoxon rank sum test. n.s., not significant

Table 3 *Postoperative clinical assessment*

	Operative procedure		
Visick grade	Angelchik prosthesis	Nissen fundoplication	P value (Angelchik *versus* Nissen)
I	15 (77)	20 (94)	n.s.
II	8	9	
III	4 (23)	2 (6)	n.s.
IV	3	0	

Mean duration of follow-up is 38 months (range 18–56) Statistical comparison is by the χ^2 analysis· n.s., not significant. Percentages are given in parentheses

when compared with pre-operative findings. There were no significant differences in the pH profiles between the Angelchik and Nissen groups either pre-operatively or postoperatively

In the Angelchik group there was a significant postoperative reduction in the percentage of time that the pH was <4 (median 14·9, range 2·4–41·6, *versus* median 1·1, range 0–27 5) ($P < 0{\cdot}05$, Wilcoxon rank sum test). The percentage of time that the pH was <4 in the Nissen group was also significantly reduced (median 11·0, range 1 0–53·6, *versus* median 0·6, range 0–17) ($P < 0{\cdot}01$, Wilcoxon rank sum test)

The total number of reflux episodes was not significantly reduced after operation in the Angelchik group (median 42, range 13–158, *versus* median 18, range 0–76), but was significantly reduced in the Nissen group (median 48, range 6–133, *versus* median 7, range 0–94) ($P < 0{\cdot}01$, Wilcoxon rank sum test).

The number of reflux episodes which were longer than 5 min in duration was not significantly reduced postoperatively in the Angelchik group (median 9, range 0–25, *versus* median 1, range 0–13), but was significantly reduced in the Nissen group (median 5, range 0–25, *versus* median 0, range 0–7) ($P < 0{\cdot}01$, Wilcoxon rank sum test).

Of the 24 postoperative pH recordings performed in the Angelchik group, 5 were abnormal compared with only 2 abnormal recordings of the 21 performed in the Nissen group.

Lower oesophageal sphincter pressure

In both the Angelchik and Nissen groups, 21 patients had pre-operative oesophageal manometry performed Postoperatively, 22 patients in the Angelchik group and 19 in the Nissen group had manometry performed; the lower oesophageal sphincter pressure (mmHg) was significantly raised in the Angelchik group (median 13, range 5–40, *versus* median 35, range 15–70) and the Nissen group (median 12, range 5–40, *versus* median 30, range 12–45) ($P < 0{\cdot}05$, Wilcoxon rank sum test). There was no significant difference between the two groups in either the pre-operative or postoperative sphincter pressures.

Complications

There was no operative mortality in either group. The spleen was removed because of intra-operative injury in one patient in each group. One patient in the Angelchik group developed a subphrenic abscess which required operative drainage and the prosthesis was removed at the second operation. One patient in each group developed a pulmonary embolus. Both made a satisfactory recovery. There was one wound infection in the fundoplication group and one wound dehiscence in the Angelchik group

Complications specific to antireflux surgery were common. Transient dysphagia was common and occurred in 17 (57 per cent) of the Angelchik patients and in 12 (39 per cent) of the fundoplication group. Dysphagia persisted beyond 3 months in six patients in the Angelchik group. Three of these had pre-operative strictures and the dysphagia was mild. In the fundoplication group no patient had persistent dysphagia. Three patients in the Angelchik group had severe persistent dysphagia without a pre-existing stricture: the prosthesis was removed in two; the third patient refused further surgery.

Gas-bloat syndrome occurred with similar frequency in the two groups: ten patients (33 per cent) in the Angelchik group and nine (29 per cent) in the fundoplication group. Gas-bloat was defined as a clinical syndrome characterized by postprandial fullness, abdominal discomfort and a feeling of distension.

Complications specific to the Angelchik prosthesis, such as erosion, migration, and disruption of the prosthesis did not occur in this series.

Discussion

While it is evident from our results and those of others that the Angelchik prosthesis can increase lower oesophageal sphincter pressure and prevent gastro-oesophageal reflux, the mechanism by which the device achieves these results is not clear. Samelson *et al* concluded from studies in a canine model that the prosthesis acted by preventing distraction of the lower oesophageal sphincter by limiting gastric wall tension in the region of the gastro-oesophageal junction[16].

This study confirms the ability of the prosthesis to control reflux as determined by 24 h pH monitoring and oesophageal manometry. These objective assessments were performed between 3 and 6 months postoperatively and even at this early stage the fundoplication provided more effective control of reflux On longer follow-up the prosthesis was again found to be less effective than fundoplication in controlling reflux, and this was confirmed clinically by the return of symptoms and by the recognition of oesophagitis at endoscopy

Complications specific to antireflux surgery were seen in both groups of patients. However, these were more common in the Angelchik group. Dysphagia made removal of the prosthesis necessary in two cases. The incidence of early dysphagia with the prosthesis in the study by Gear *et al* was 38 per cent and resolution of the dysphagia occurred in all but two of his cases within a few months[2] On the other hand Wale *et al.* reported a 41 per cent incidence of long-term residual dysphagia[5]. We have found that more than half the patients experience some dysphagia after insertion of the prosthesis. However, the majority settle within a few months. In this series, 10 per cent had persistent dysphagia severe enough to warrant removal of the prosthesis, and of cases with pre-operative stricture only a minority obtained relief of their dysphagia. This is in contrast with the fundoplication group, in which no patient experienced severe persistent dysphagia and all those with pre-operative dysphagia obtained some relief of their symptoms.

Complications specific to the Angelchik prosthesis, such as migration and erosion into the gastrointestinal tract, have been widely reported by others but did not occur in this series.

Migration of the prosthesis has been reported by a number of authors[17,18] Migration has been of two types: proximal migration into the chest where angulation of the prosthesis may cause acute dysphagia, and detachment of the tapes, which allows displacement into the peritoneal cavity[19] The risk of proximal migration may be minimized by crural repair and detachment of the tapes has not been reported since the prosthesis was redesigned so that the tapes are attached along the circumference of the device.

Erosion of the prosthesis into the lumen of the alimentary tract has also been reported. This problem appears to arise in two situations. The majority have occurred when the prosthesis is placed adjacent to an alimentary tract suture line[20]. The risk is also present if the prosthesis is used after failure of a previous antireflux operation when, in the course of a difficult dissection, the abdominal oesophagus may undergo some trauma[21] The recommendation, therefore, by Durrans *et al.*, on the use of the prosthesis when previous surgery has failed should be treated with caution[22].

The effects of long-term implantation of prosthetic material in the abdominal cavity must also be considered. The longest reported follow-up of the Angelchik prosthesis comes from

Angelchik *et al.*[23]. No problems have emerged 10 years after implantation.

In this series, the Nissen fundoplication gave better results than the Angelchik prosthesis. Nissen fundoplication provided more permanent control of gastro-oesophageal reflux and dysphagia was less frequent and less persistent. However, complications of the Angelchik prosthesis such as migration and erosion can be avoided by proper case selection and careful operative technique.

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Near-total thyroidectomy for carcinoma of the thyroid

There is controversy about the most appropriate treatment for patients with thyroid cancer. This study analyses our experience with 206 cases of thyroid cancer from an endemic goiterous area. There were 100 males and 106 females; patients presented at an earlier age with a short history. Thyroid cancers demonstrated an aggressive biological behaviour with an advanced stage at presentation (overt cancers in 51 per cent) and a relentless course with a mortality rate of 24·2 per cent for the well-differentiated tumours. Near-total thyroidectomy was performed in 126 patients. Multicentric foci of tumour were seen in 17·2 per cent of the well-differentiated cancers and 25·2 per cent of the cases of well-differentiated cancers who underwent near-total thyroidectomy developed loco-regional recurrence. Hemithyroidectomy was performed in 35 patients who refused completion total thyroidectomy at a second stage; 16·7 per cent of these patients developed a recurrence in the remaining contralateral lobe. Thus in our patients from an endemic goiterous area, near-total thyroidectomy is the treatment of choice particularly because of the frequent occurrence of follicular and anaplastic cancers (in 44·2 per cent) and because the course of the disease is more virulent.

Keywords: Thyroid carcinoma, total thyroidectomy

A. K. Sarda, S. Bal and M. M. Kapur

Department of Surgery, All India Institute of Medical Sciences, New Delhi 110 029, India

Correspondence to: Dr A. K. Sarda, 27 RPS, Triveni-I, New Delhi 110 017, India

Carcinoma of the thyroid gland represents a spectrum of disorders differing in histological appearance and clinical behavior The surgical treatment for differentiated thyroid cancers varies from extremely radical[1] to conservative[2]. Controversy centres on the question of whether total thyroidectomy is required for adequate treatment of the differentiated cancers of the thyroid. The high incidence of multicentric foci in both papillary and follicular cancers[3] and the availability of radioactive iodine for both scanning and treatment of persistent or recurrent disease[4] are the reasons cited by proponents of the radical approach. However, advocates of a less radical approach believe that multicentric deposits of tumours within the thyroid can be ignored without clinical significance with a reported cancer recurrence rate of only 4·2 per cent in the remaining thyroid tissue following lobectomy[5] Further, they believe that total thyroidectomy may be accompanied by a significant morbidity rate, with a reported complication rate as high as 30 per cent[6]. Crile used the argument of the benign behaviour of thyroid tumours and the success of adjuvant thyroxine therapy ('thyroid feeding') for the residual gland as factors favouring a conservative approach for treatment of thyroid cancers[2].

The present study is a retrospective analysis of near-total thyroidectomy as a therapeutic modality for carcinomas of the thyroid gland. This study was necessitated by the finding, reported earlier[7], that thyroid cancers in our patients in north India have a greater degree of biological aggressiveness.

Patients and methods

The catchment area of the patients in the present series was the sub-Himalayan plains and areas in and around Delhi which are recognized iodine deficient areas[8] From 1970 to 1985, 206 thyroid cancers were treated by a single surgical service representing 17 4 per cent of all thyroid disorders managed during the period under review. Data of 163 patients have been presented earlier[8], this study includes the cases which were under review by the pathologist plus the cases operated on between 1983 and 1985

In the present study thyroid cancers, whether presenting as solitary nodules or as multinodular goitres, were classified as overt cancers if there was evidence of local invasion, lymph node involvement, recurrent laryngeal nerve palsy and/or distant metastasis. Malignancy was suspected if a thyroid swelling was accompanied by complaints of a recent, rapid increase in size and had a firm to hard consistency with or without pain and pressure symptoms, this is of particular relevance because of the large number of nodular goitres presenting to our outpatient department Patients with clinically benign solitary nodules and multinodular goitres in whom carcinoma was found on histology were also included. Before 1983 all cases of solitary thyroid nodules were operated on; since 1983 fine needle aspiration biopsy is routinely performed in all nodular goitres. Patients with reports of suspicious or positive aspirates for malignancy are operated on; other indications for operation being cosmesis and pressure symptoms.

Treatment of the differentiated thyroid carcinomas aimed at near-total thyroidectomy, i e both lobes and the isthmus were excised surgically and only a rim of posterior capsule was left around the parathyroid glands and the recurrent laryngeal nerve (which was identified routinely) on at least one side that was clinically free of disease. The operation was performed as a one-stage procedure in cases where thyroid cancer was documented before operation by histological or cytological examination In patients with a more uncertain diagnosis, especially those presenting as solitary thyroid nodule, a hemithyroidectomy (affected lobe plus the isthmus) was performed with completion of near-total thyroidectomy after receipt of histopathological results usually 7–10 days after the first operation The advantage of this procedure is that the adhesions are not fibrous and tissue planes can easily be identified. Completion of total thyroidectomy was not performed in those patients who after hemithyroidectomy refused a second operation A less radical procedure was performed in patients who presented with thyrotoxicosis and apparently benign multinodular goitres solely because in these cases carcinoma was a histological surprise, none of these patients had a completion of total thyroidectomy. Locally advanced cancers were merely biopsied

Results

The age and sex distribution of the 206 cases of thyroid cancers in the study group have been shown in *Figure 1*. The male to female ratio was 1:1·1 The average age of presentation was 39·7 years Thyroid enlargement was the commonest mode of presentation (90 per cent) and the average duration of this was 7 8 years (1 month to 20 years). Pressure symptoms (dysphagia

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and dyspnoea) in 24 per cent and hoarseness in 22 per cent with a tender thyroid gland were seen frequently, especially with anaplastic cancers. Unilateral vocal cord palsy was recorded in five patients at presentation. Many patients (51 per cent) presented with overt cancers (*Table 1*).

Histopathologically papillary carcinoma constituted the predominant group (44·7 per cent); follicular carcinomas (28·0 per cent), medullary carcinomas (12·1 per cent), anaplastic carcinomas (11·2 per cent) and squamous cell carcinomas (3·9 per cent) occurred in the rest of the patients. A routine examination of the histopathological material revealed multicentric foci in 17 2 per cent of the cases.

At presentation lymph node metastases were recorded in 45·1 per cent of the cases (37·0 per cent of papillary and 34·5 per cent of the follicular carcinomas). Distant metastases had occurred in 27·6 per cent of the cases; lungs and the skeletal system were the most common sites for spread of the differentiated thyroid cancers.

Near-total thyroidectomy was performed in 62·1 per cent of the cases; in 19 cases the procedure was completed at a second stage. Among the 40 cases (19·4 per cent) who underwent hemithyroidectomy, 52·5 per cent were papillary and 22·5 per cent were follicular carcinomas (*Table 2*). Only one patient who underwent near-total thyroidectomy, died in the immediate postoperative period because of an associated cardiac disorder. Hypoparathyroidism was observed in 15/126 (11·9 per cent) but only four patients (3 2 per cent) required permanent supplement therapy. Permanent unilateral recurrent laryngeal nerve injury occurred in 5/126 (4·0 per cent). Since all patients with thyroid cancers routinely received suppressive doses of thyroxine after operation hypothyroidism did not occur. Only 1/35 cases (3·0 per cent) who underwent hemithyroidectomy developed unilateral recurrent laryngeal nerve palsy (*Table 3*).

In the patients who underwent hemithyroidectomy, recurrence in the remaining contralateral lobe was seen more frequently in cases of follicular carcinomas (*Table 4*). Loco-regional recurrence occurred more commonly in patients with papillary carcinomas. Mortality was high in all the histological types of thyroid tumours. Among the differentiated cancers 2/21 of papillary and 2/9 of follicular cancers who underwent hemithyroidectomy died, while 7/65 of papillary and 10/37 of follicular cancers who underwent near-total thyroidectomy died during the follow-up period. The difference was not statistically significant.

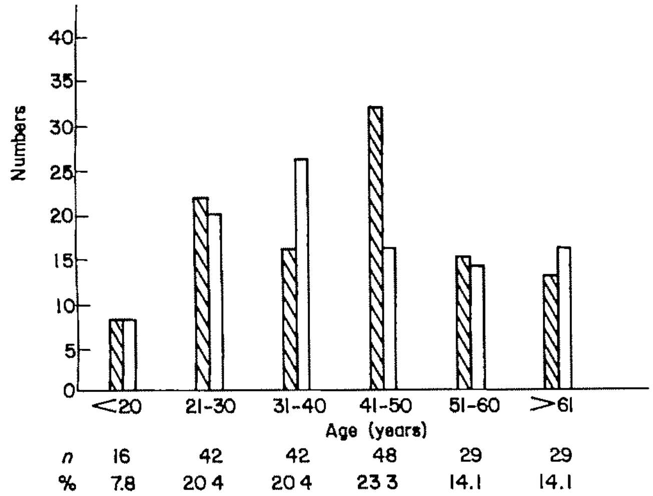

Figure 1 *Age and sex distribution of 206 cases of thyroid cancers.* ▨, *Females (106),* ☐, *males (100). The number of patients and percentage of total patients in each age category is given*

Table 1 *Presentation of 206 cases of thyroid cancers*

Type of cancer	Solitary thyroid nodule	Multinodular goitre	Overt	Suspicious	Toxic
Papillary	32	14	37	6	3
Follicular	12	13	26	6	1
Medullary	4	0	19	2	0
Anaplastic	3	1	18	1	0
Squamous cell	2	0	5	1	0
Total	53	28	105	16	4

Discussion

The catchment area of the patients under study was the sub-Himalayan plains which are recognized iodine deficient areas[8]. Although thyrotrophin (TSH) has been considered to be an initiating factor for carcinoma of the thyroid in reports from endemic areas[9], the role of TSH in the pathogenesis of thyroid cancer remains obscure despite the finding of significantly higher levels of TSH in the carcinoma group[7]. However, reports

Table 3 *Complications of 126 cases of near-total thyroidectomy*

Operative mortality	1
Hypoparathyroidism	15 (4)*
Unilateral recurrent laryngeal nerve palsy	5†

* Four patients permanently affected; † operative injury, excludes five patients with pre-operative nerve palsy

Table 4 *Follow-up of the 150 cases of well-differentiated thyroid cancers (average follow-up 10·6 years, range of follow-up 3 to 15 years)*

	Papillary	Follicular	*P* value*
Contralateral lobe recurrence	2/21	3/9	n.s
Loco-regional recurrence†	23/70	6/45	$<0{\cdot}001$
Mortality	14/91	22/58	$<0{\cdot}001$
Lost to follow-up	1		

* Calculated by χ^2 test; † excludes patients who underwent hemithyroidectomy or biopsy

Table 2 *Treatment of 198 cases of thyroid cancers (excluding squamous cell carcinoma)*

Type of cancer	Number	Hemithyroidectomy	Near-total* thyroidectomy	Sub-total thyroidectomy	Biopsy
Papillary	92	21	65	5	1
Follicular	58	9	37	8	4
Medullary	25	3	16	6	0
Anaplastic	23	2	8	2	11
Total	198	35	126	21	16

* Includes 19 cases of hemithyroidectomy converted to near-total thyroidectomy at a second operation

from endemic areas indicate a difference in the clinical and pathological features of thyroid cancers from those occurring in the iodine replete areas[8]. These features are evident from the present study where thyroid cancers occurred in younger patients and the history was shorter. A large percentage of the patients presented with advanced, fast-growing tumours In addition, there was a distinct histopathological difference in the type of these tumours when compared with reports from non-endemic areas; there being more follicular and anaplastic carcinomas with a consequent smaller proportion of papillary tumours. The aggressive clinical behaviour of the tumours is evident from the relentless progression of the disease and the high mortality among all histological types of thyroid cancers in this study. This finding is also reported by authors from other endemic areas[10] A plausible explanation for the aggressive biological behaviour of thyroid cancers in endemic areas may be found in reports by Crile[11,12], who suggested that continued TSH stimulation of these tumours may lead to transformation of differentiated, slow-growing, endocrine-dependent tumours to rapidly growing, autonomously functioning, metastasizing tumours. Keeping this natural history of thyroid cancers in our patients in perspective, we aimed always at near-total thyroidectomy for all histological types We also suggest that, especially in endemic areas with a high circulating level of TSH, an initial aggressive surgical approach for these tumours should be applied even when they present at an early stage of the disease.

Multicentricity is another important indication for total thyroidectomy in the population under study and is relevant for both follicular and papillary tumours[3,13]. Its incidence varies from 20 to 80 per cent in different series depending on the perseverence of the pathologist[14]; a routine examination of the excised specimens in our patients revealed multicentric foci in 17·2 per cent of the well-differentiated tumours. Further, 16·7 per cent of the patients who underwent hemithyroidectomy in the study group developed recurrence in the remaining contralateral lobe This recurrence rate is usually reported as between 3 and 8 per cent, but has been reported as high as 24 per cent[15]. The significance of this finding is emphasized by Tollefsen *et al.*[16], who found that most deaths from papillary carcinoma resulted from persistent or recurrent disease in the neck after initially inadequate surgical treatment.

An additional factor favouring total thyroidectomy is the reported transformation from well-differentiated tumours to anaplastic and squamous cell carcinomas[17–19] which are recognized for rapid growth, local invasion and a shortened life expectancy. Follicular carcinomas are reported to be more commonly associated with anaplastic tumours. We have earlier reported this association in cases of squamous cell carcinomas[20]. Further, thyroglobulin$^{(Tg)}$ levels can be used after total thyroidectomy to screen for recurrent or persistent disease[21].

The risk of an increased complication rate is sometimes considered a contra-indication to total thyroidectomy[22–24]. Recurrent nerve damage is reported at an incidence of up to 23 per cent[22] and hypoparathyroidism in up to 29 per cent[25]. The habit of performing near-total thyroidectomy with preservation of the posterior capsule has minimized complications[4,25] Using this operative technique we observed recurrent laryngeal nerve damage in 4·0 per cent and permanent hypoparathyroidism in 3·2 per cent of our patients who underwent near-total thyroidectomy

The added advantage of near-total thyroidectomy for patients from poorer socio-economic strata in our study is the ability to perform an immediate postoperative evaluation of disseminated disease with radioactive iodine and to implement treatment This is important as we find that many of the patients are irregular in follow-up and when they return with recurrence, the disease may be so advanced as to negate the value of further therapy This is an innate problem of all developing countries and any management plan must be not only clinically optimal but also take account of the socio-economic and cultural characteristics of the population.

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Contrast enhanced CT scan as a diagnostic procedure in mesenteric ischaemia due to mesenteric venous thrombosis

P.-A. Clavien, O. Huber, D. Mirescu* and A. Rohner

*Department of Surgery and *Radiology, University Hospital, 1211-4 Geneva, Switzerland*
Correspondence to: Dr P.-A. Clavien

Mesenteric infarction resulting from mesenteric venous thrombosis is a difficult diagnosis which should be differentiated from other causes of bowel infarction[1]. Clinical presentation and intra-operative findings are often characteristic[1,2]. Most authors stress the importance of arteriography to assess the aetiology of mesenteric infarction and define the site of arterial occlusion[3–5]. However, mesenteric venous thrombosis is often not recognized at arteriography and appears difficult to distinguish from non-occlusive infarction. Contrast-enhanced CT scan, which has been demonstrated as useful in the evaluation of portal thrombosis[6] or portal cavernoma[7], represents an interesting and non-invasive alternative for the diagnosis of venous mesenteric infarction[8].

We report four cases of mesenteric infarction which have been diagnosed by contrast-enhanced CT scan, either pre-operatively (case 1 and 2), to confirm an intra-operative diagnosis (case 3), or as a means of follow-up of conservative therapy (case 4).

Patients

Case 1

A 29-year-old man, HIV seropositive and a morphine addict, presented with a 5-day history of cramping abdominal pain and vomiting. Two weeks previously a splenectomy was performed for an immune thrombocytopenia resistant to medical treatment. On examination, he was ill, febrile to 38°C and had an abdomen which was diffusely tender. Initial investigations revealed a white cell count of 32×10^9/l with 87 per cent polymorphonuclear leucocytes and a normal platelet count. A contrast-enhanced CT scan performed in search of an intra-abdominal abscess showed typical findings of venous mesenteric infarction: namely a mesenteric venous thrombosis (*Figure 1a*), thickening of the intestinal wall, a valvulae conniventes localized to an ileal loop and ascites (*Figure 1b*). The diagnosis was also confirmed by selective angiography and subsequent laparotomy. He was successfully treated by wide resection (60 cm of ileum) and intravenous heparin in therapeutic doses. Furthermore, an isolated and persistent protein S (a protein C cofactor) deficiency of <20 per cent was demonstrated.

Case 2

A 44-year-old man, treated in the last 4 years for chronic pancreatitis, was referred with abdominal pain, haematemesis and splenomegaly. Examination revealed slight tenderness and guarding of the upper abdomen with diminished bowel sounds. The white cell count was 18×10^9/l associated with an erythrocyte count of 5500×10^9/l. Gastroduodenoscopy was normal. A contrast-enhanced CT scan showed massive splenomegaly, pancreatic calcification, a small pseudocyst in the pancreatic tail, portal and mesenteric venous thrombosis, portal cavernoma, thickening of a middle jejunal loop, and peritoneal fluid. Laparotomy demonstrated haemorrhagic ascites and venous mesenteric infarction involving about 70 cm of jejunum. The patient was successfully treated by wide intestinal resection and full dose heparin anti-coagulation. Later on, haematological investigations revealed a polycythaemia rubra vera.

Case 3

A 75-year-old man presented with a 1 week history of intermittent upper abdominal pain associated with bloody diarrhoea. Two years previously he had complained of the same symptoms. At this time, despite extensive investigations which included gastroduodenoscopy, colonoscopy, barium meal and enema, the diagnosis remained elusive and he was treated conservatively. On admission, physical examination revealed a distended abdomen with slight diffuse tenderness and absent bowel sound. The white cell count was 9×10^9/l. Except for a plain abdominal X-ray no pre-operative investigation was performed. At laparotomy a sero-sanguineous peritoneal fluid and typical venous mesenteric infarction involving 60 cm of proximal ileum were found; a wide resection was undertaken. Twelve hours postoperatively a contrast-enhanced CT scan clearly showed a mesenteric venous thrombosis which confirmed the intra-operative macroscopic diagnosis. With full-dose intravenous heparin treatment, the postoperative course was uneventful. No predisposing factors could be found in this patient.

Case 4

A 54-year-old Italian with a history of multiple admissions for deep

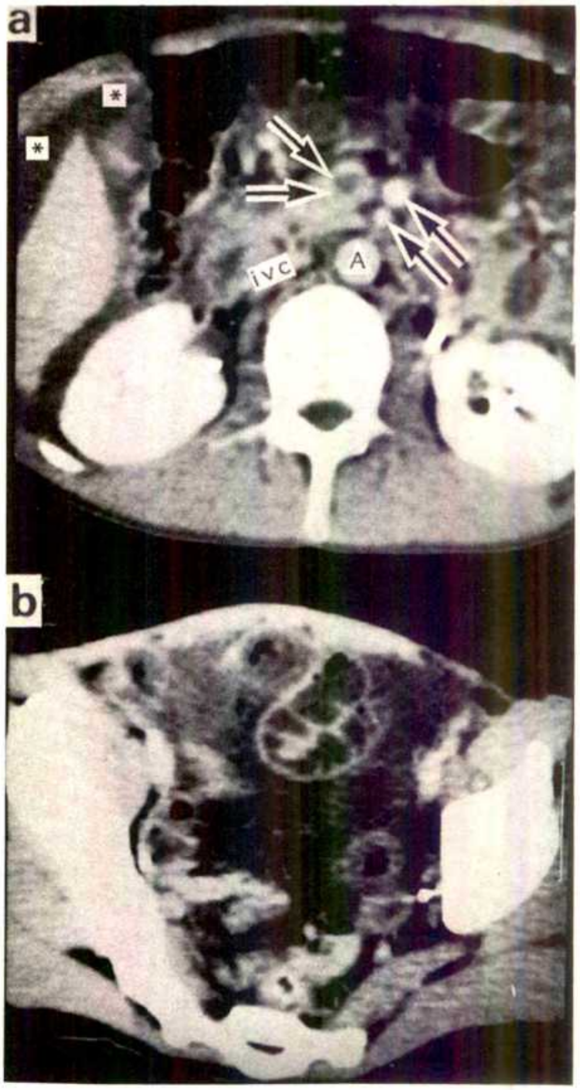

Figure 1 *Contrast-enhanced CT scan showing* **a** *thrombosis of the superior mesenteric vein (arrows) and* **b** *ascites around an ileal loop with thickened intestinal wall and valvulae conniventes corresponding to a venous jejuno-ileal infarction. Arrowheads, superior mesenteric artery; A, aorta; ivc, inferior vena cava; *, ascites*

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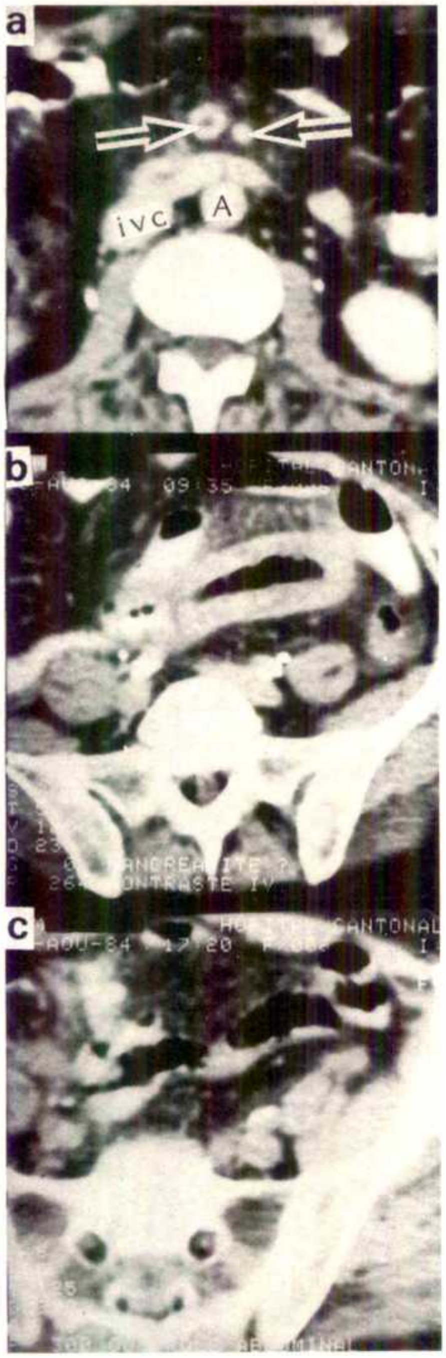

Figure 2 *Contrast-enhanced CT scan showing* **a** *thrombosis of the superior mesenteric vein (arrow);* **b** *important thickening of a small bowel loop; and* **c**. *2 weeks later, total regression of the bowel wall thickening. Arrowhead, superior mesenteric artery; A, aorta; ivc, inferior vena cava*

vein thrombosis and pulmonary emboli was admitted with several months of intermittent upper abdominal pain with nausea, vomiting, and diarrhoea. On examination the patient had a low-grade fever and his abdomen was diffusely distended. Occult blood was found in the stool. The white cell count was 19×10^9/l. Plain abdominal X-ray was uncharacteristic and endoscopy showed grade 2 oesophageal varices. A contrast-enhanced CT scan showed a portal and mesenteric venous thrombosis (*Figure 2a*) with thickening of a middle jejunal loop (*Figure 2b*). On conservative treatment, serial CT scans showed regression of the jejunal thickening which had totally disappeared 2 weeks later (*Figure 2c*). Anticoagulation in therapeutic doses was contra-indicated on the grounds of persistent oesophageal varices. During the following 2 years he presented with two similar episodes which were both treated conservatively and documented by serial CT scans. Recently, he had the first episode of acute bleeding from oesophageal varices which were treated by sclerotherapy. A liver biopsy confirmed the absence of cirrhosis. A persistent AT III deficiency to <60 per cent was found. Screening of the patient's family for AT III was not possible. Thus, it remains unclear if this deficiency was congenital or acquired.

Discussion

Clinical presentation of mesenteric infarction due to mesenteric venous thrombosis is suggestive of the diagnosis when a history of deep vein thrombosis or lung emboli with long and intermittent abdominal pain are present[1-2]. On examination, mesenteric venous thrombosis is not distinguishable from other causes of infarction[1]. Arteriography is indicated when an arterial aetiology is suspected as it undoubtedly offers the best assessment of the mesenteric vascular anatomy, which is useful if revascularization is necessary[3-5]. However, knowledge of the precise anatomy of venous thrombosis is not necessary since revascularization is not indicated in venous mesenteric infarction[1,2,5]. In addition, visualization of the venous thrombosis at arteriography requires an experienced radiologist and is time consuming[1,8-10].

Contrast-enhanced CT scan is a non-invasive modality which represents an interesting alternative to arteriography. Mesenteric venous thrombosis is easily recognized, presenting with hypodensity in the trunk of the superior mesenteric vein, and its association with peritoneal fluid, thickening of the intestinal wall and valvulae conniventes localized to a jejuno-ileal segment constitute a typical triad for venous mesenteric infarction. When the diagnosis is clinically suspected, CT scan should be performed as an emergency procedure in order to confirm the diagnosis. If the above triad is present, further investigations are unnecessary before laparotomy. Most commonly, the venous aetiology is only suspected at laparotomy on the basis of serosanguineous peritoneal fluid, typical appearance of the gut and its mesentery with normal arterial pulsations[1,2]. Contrast-enhanced CT scan appears to be the procedure of choice to confirm the diagnosis postoperatively. Case 4 illustrates that, in case of conservative treatment, serial CT scans can be extremely useful to monitor the evolution of the affected bowel. Furthermore, CT scan aids in the detection of other important intra-abdominal conditions which represent predisposing factors, namely liver cirrhosis, intra-abdominal abscess, acute and chronic pancreatitis.

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Facial paralysis due to a benign parotid tumour

D. Whillis, J. R. Goepel and A. J. Shorthouse*

*Weston Park Hospital and *Royal Hallamshire Hospital, Sheffield, UK*

Correspondence to: Dr D. Whillis, Weston Park Hospital, Sheffield S10 2SJ, UK

Traditional surgical teaching is that in cases of parotid swelling, facial nerve involvement is 'proof positive' of carcinoma[1]. This is misleading[2-8], and leads to an unduly confident diagnosis of malignancy in the absence of pathological support. We report a patient with a parotid swelling and paresis of the ipsilateral facial nerve; the lesion subsequently proved to be benign. A cause for the paresis is postulated and other similar cases from the literature are reviewed. We now consider pre-operative assessment, despite its difficulties, essential in the management of patients with a parotid swelling.

Case report

A 67-year-old woman presented with a 1 week history of left facial weakness and associated nerve root pain. A painless left pre-auricular swelling had been present for 4 months. On examination, there was a 6 × 4 cm firm mass in the left parotid region, fixed deeply but not to skin. There was no associated lymphoadenopathy. In addition, there was an obvious left lower motor neurone VII nerve palsy affecting all branches of the nerve. In view of the associated facial paralysis, a clinical diagnosis of a malignant parotid tumour was made.

A radical total parotidectomy was performed. The mass was confined to the deep part of the parotid gland without local infiltration so it was removed with a wide excision taking in adjacent lymph nodes, the upper part of sternomastoid and the posterior part of the masseter muscle. The facial nerve was divided near its exit from the skull.

Pathology

The parotid gland was partly replaced by a cystic mass containing thick yellow-green pus. Histological examination showed a Warthin's tumour with marked cystic change and partial necrosis. Focal squamous metaplasia was present, in places associated with dense fibrosis of the stroma. Large nerves were stretched around the margin of the cyst between it and the remaining salivary tissue. Small nerve branches showed degeneration where trapped in fibrous or inflammatory tissue. The cyst contained neutrophil polymorphs and Gram-positive organisms. There was no evidence of malignancy.

Discussion

There is a traditional triad of physical signs associated with parotid swellings, any one of which is considered adequate for the clinical diagnosis of malignancy[2]. These are: (1) demonstrable metastases, (2) invasion of adjacent structures, and (3) spontaneous facial palsy. Although facial palsy is considered to be a reliable physical sign, there are six previous reports of facial nerve paralysis occurring with benign parotid tumours. In one case, nerve damage was caused by haemorrhage into a cyst[3]; the authors postulated increased pressure on the facial nerve. In most of the other cases the tumour was a pleomorphic salivary adenoma with or without cystic change[4-6]; in another case it was an oncocytoma[7].

There is only one other report of a facial palsy associated with a Warthin's tumour[8], and we believe the pathogenesis in our case to be similar. We consider that infection occurred in an infarcted cystic adenolymphoma, with nerve damage occurring as a result of stretching the nerve round the cyst and additional inflammation and infarction.

We now favour pre-operative assessment of parotid swellings despite the difficulties, which are mainly those of distinguishing between benign and malignant tumours. Parotid sialography is of limited value[9] and, although computed tomography is accurate in detecting tumours in and around the parotid, it is unable to distinguish between benign and malignant lesions[10]. Peroperative frozen section diagnosis is not completely reliable owing to sampling errors or the co-existence of more than one pathological entity[8,11]. Also dissemination of tumour cells may occur, increasing the risk of local recurrence. This is not the case, however, with fine needle aspiration biopsy; although there is the risk of a false negative result[12] the procedure is simple and without significant morbidity. Ultrasonography may be of value in pre-operative assessment, and indeed the appearance of adenolymphoma may be characteristic[13]. Occasionally open biopsy with subsequent delayed primary surgery may be required.

At the present time we would recommend fine needle aspiration and ultrasound examination in all cases of parotid swellings presumed to be malignant on the basis of facial nerve palsy. The rare occurrence of a benign cystic swelling might be identified, and if needle aspiration is performed may also allow recovery of the palsy. A careful dissection with preservation of the nerve might also be followed by some recovery of function.

Where the diagnosis remains doubtful, the tumour must be assumed malignant. Despite the remote possibility of benign disease, a radical parotidectomy with sacrifice of the facial nerve should be performed. The presence of facial nerve paralysis in a malignant parotid tumour is a poor prognostic sign[14], and significant efforts should be made to avoid the considerable problems of locally recurrent disease.

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Plunging salivary glands

J. D. Maynard

Medical and Dental School, Guy's and St. Thomas' Hospitals, Gordon Museum, Guy's Hospital, London SE1 9RT, UK
Correspondence to: Mr J. D. Maynard

Patey[1] first drew attention to the disappearing parotid tumour. As he pointed out, the 'plunging goitre' is a familiar phenomenon. The goitre partly lying in the mediastinum rises into the neck on deglutition and particularly on forced expiration against a closed glottis.

Five years ago the author was confronted with a parotid tumour that disappeared under anaesthetic and 4 years ago with a 'plunging' submandibular salivary gland. Two months ago a 3 cm hard mobile parotid tumour disappeared between the ward and theatre.

Case reports

Case 1

A man aged 70 years was seen with a discrete mobile and rather soft lobulated mass measuring 3 × 2 cm in the lower pole of the right parotid. A possible diagnosis of adenolymphoma was made and admission arranged.

When the patient was seen in the anaesthetic room after the induction of general anaesthesia, the tumour had disappeared. After checking the patient's notes and, fortunately, being aware of Patey' s experience, we explored the right parotid through a routine parotidectomy incision. The facial nerve was identified at its bifurcation and the apparently normal lower pole of the parotid was mobilized. During this manoeuvre the tumour reappeared from behind and deep to the angle of the jaw. It was apparent that the tumour was arising from the lower part of the deep lobe of the parotid. Thus, forewarned that the lower branch of the VIIth nerve would be superficial to the tumour, this branch was dissected without injury and the lower part of the deep lobe and the lower half of the parotid was excised with the contained tumour. There was no postoperative facial palsy and histology confirmed that the tumour was an adenolymphoma. There were no other complications.

Case 2

A man aged 31 years was found to have a hard discrete mobile swelling measuring 3 cm in diameter just anterior to the left submandibular gland. It was thought to be a submandibular lymph node or even a rare submandibular gland neoplasm. It was explored at another hospital and the left submandibular gland excised without incident. The next morning the swelling was still present. The excised salivary gland, although large, was normal. The patient was referred for a second opinion and reoperation was requested.

At operation an incision was made over the tumour and extended posteriorly into the previous incision. After incising the platsyma, the tumour disappeared and the operative site appeared completely empty. A finger was inserted into the mouth and the tumour was found under the mucosa of the floor of the mouth. It was easily displaced into the submandibular wound and removed without difficulty. Microscopically, it was found to be a neurofibroma. There were no postoperative complications.

Case 3

A 56-year-old woman was seen in out patients with a 3 cm hard mobile mass in the lower pole of the right parotid gland. She thought it had been there for at least 18 months, but had a vague idea it had been present before this but had disappeared. We unwisely discounted this information.

When the patient reached the operating theatre no tumour was palpable in her apparently normal parotids. The notes confirmed the side of the vanishing tumour and the gland was explored. Before identification of the VIIth nerve there was again no evidence of tumour on repeated palpation. The nerve was identified and forward mobilization of the superficial lobe of the gland commenced. At this stage it became apparent that there was a mass deep to the main branch and bifurcation of the facial nerve. On further traction a deep lobe tumour, anterior and deep to the styloid process, was defined and once more became the obvious superficial tumour that had presented clinically in the out patients. It was excised with the lower pole of the parotid. There were no postoperative complications and the VIIth nerve was intact. Histological examination showed the tumour to be a pleomorphic adenoma.

Discussion

Patey, having previously described the dumb-bell tumour of the parotid[2], in which a deep tumour becomes imprisoned in the lateral pharyngeal space, considered that the tumour in his case had so stretched the margins of the space as to present superficially. The muscular relaxation under general anaesthetic had allowed the tumour to retreat to the site of origin and apparently disappear. The same explanation suffices for the two parotid tumours described here.

The submandibular tumour had arisen in the region of the sublingual gland in the floor of the mouth superior to the mylohyoid but had prolapsed behind the free posterior border of the mylohyoid and became visible and palpable in the submandibular region inferior to the muscle. The muscular relaxation consequent on general anaesthesia had allowed the tumour to slip out of the operative field to the superior surface of the mylohyoid where it was readily palpable in the floor of the mouth.

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Pseudoachalasia after radical gastrectomy

L. J. Yeoman, A. Grundy, M. C. O. Parker* and A. G. T. W. Fiennes*

*Departments of Diagnostic Radiology and *Surgery, St. George's Hospital, Blackshaw Road, London SW17 0QT, UK*

Correspondence to: Dr A. Grundy

Pseudoachalasia, or secondary achalasia, is a rare condition suggestive of underlying malignancy in which the oesophagus shows abnormalities identical to primary idiopathic achalasia with respect to the clinical, radiographic, endoscopic and manometric findings. The malignancy is usually an adenocarcinoma of the stomach or, less commonly, a non-gastrointestinal malignancy[1–16].

We report the case of a patient who had a radical total gastrectomy with oesophagojejunostomy for an adenocarcinoma of the stomach. This patient subsequently demonstrated radiological and endoscopic features of achalasia, although these were not present at the time of presentation of the carcinoma.

Case history

A 69-year-old man presented with breathlessness and anaemia. A double-contrast barium meal revealed a tumour high on the lesser curve of the stomach, which was confirmed by endoscopic biopsy to be an adenocarcinoma.

A radical total gastrectomy, splenectomy and distal pancreatectomy with omentectomy was performed. A stapled oesophagojejunal anastomosis with a Roux-en-Y loop was fashioned. Histological examination of the resected specimen showed a moderately differentiated adenocarcinoma. The resected margins were free of tumour but lymph nodes from the greater curve and lesser curve contained metastatic tumour.

The patient remained well until 6 months later when he was re-admitted to hospital with postprandial vomiting. There was no dysphagia and appetite was preserved, although weight loss of 5 kg over the preceding month was documented.

A barium meal demonstrated a functional obstruction of the lower oesophagus with a smoothly tapered narrow segment, which opened only when an adequate column of barium produced sufficient pressure (*Figure 1*); the appearances resembled achalasia. There was no evidence of stricture at the anastomosis or of tumour recurrence and barium passed freely into the jejunal loop.

At endoscopy the lower oesophagus was thought to be slightly rigid but otherwise normal. The jejunum was entered easily and appeared normal. Biopsies from the anastomosis and adjacent mucosa showed no evidence of malignancy or inflammation.

Balloon dilatation of the distal oesophagus was performed and the lower oesophagus dilated readily. A repeat barium swallow 6 days later showed some improvement with less lower oesophageal spasm, although the appearances still resembled achalasia.

A small bowel meal via a tube introduced into the efferent loop suggested extrinsic compression 15 cm from the anastomosis site. At laparotomy there was extensive peritoneal disease with encasement of the lower end of the oesophagus by plaque-like tumour. There was no possibility of palliative surgery.

The patient died postoperatively and post-mortem examination was not performed.

Discussion

Primary achalasia is a motility disorder of the oesophagus of unknown cause.

On barium studies achalasia has characteristic features. There is failure of relaxation of the lower oesophageal sphincter with the lower end showing smooth symmetrical narrowing. In the horizontal position barium does not pass into the stomach, but in the upright position the barium column is retained above the lower oesophageal sphincter until its hydrostatic pressure overcomes the resistance and barium squirts into the stomach.

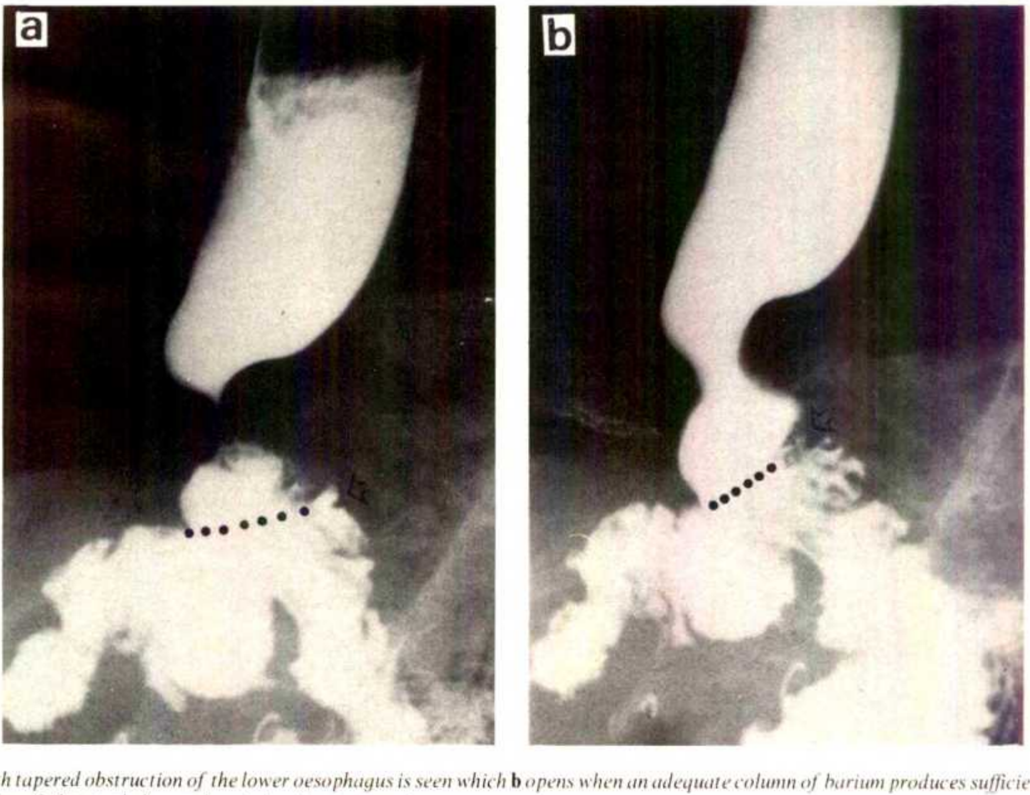

Figure 1 **a** *Smooth tapered obstruction of the lower oesophagus is seen which* **b** *opens when an adequate column of barium produces sufficient pressure. Dots indicate the position of the stapled oesophagojejunal anastomosis*

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However, the sphincter closes before the oesophagus is empty. There is a reduction in peristalsis, initially in the lower two-thirds and eventually throughout the oesophagus, although unco-ordinated contractions may be seen. The oesophagus is usually dilated to a variable degree[17,18].

At endoscopy the oesophagus is usually dilated and aperistaltic and the endoscope passes easily into the stomach through the lower sphincter[19].

In secondary achalasia the above characteristics are mimicked, but the condition is temporally and apparently causally associated with a malignancy[1]. This is most commonly adenocarcinoma of the stomach[1–10], but has been described with gastric lymphoma[12], bronchogenic carcinoma[1,11,13], carcinoma of the pancreas[1], hepatoma[11], carcinoma of the prostate[14], Hodgkin's disease[15] and reticulum cell sarcoma[16]. In cases of secondary achalasia associated with gastric carcinoma it may be difficult or impossible to detect the presence of the malignancy on barium study, endoscopy or even manometry. Inhaled amyl nitrite after barium swallow has been used to help distinguish achalasia from pseudoachalasia as the lower sphincter relaxes in the primary but not in the secondary form[20].

In our patient the past history of adenocarcinoma of the stomach was known. However, in patients who present *de novo* with achalasia malignancy must be considered.

Secondary achalasia, which has a functional neuromuscular basis, must not be confused with the effects of an organic mechanical obstruction due to annular infiltration or a mass. In this situation, unlike achalasia, peristalsis is present and can be seen during barium swallow. Also the narrowed segment is rigid and does not distend with the transition zone between normal and abnormal oesophagus being sharply defined. The mucosa may be ulcerated and a tumour mass may be seen[18]. It has been suggested that swallowing an effervescent agent after the barium helps in the distinction between functional and mechanical obstruction as the oesophagus will then empty in the former but not in the latter[18]. At endoscopy the endoscope will not pass through, or will only do so with some difficulty when severe narrowing is of organic origin rather than functional[19].

The pathophysiology of secondary achalasia is unclear. Several mechanisms have been proposed: a non-specific reaction to obstruction; carcinomatous involvement of the oesophageal myenteric plexus; invasion of the vagus nerve or its dorsal nucleus; or a paraneoplastic effect equivalent to peripheral neuropathy and central nervous system syndromes seen with certain carcinomas, not due to direct invasion or metastases[2,3,11].

The treatment of secondary achalasia is aimed at the primary tumour and patients have been reported in whom a return of peristalsis has followed surgery, radiation therapy and chemotherapy[6,12,13,16] although such improvement is not invariable[15]. It would appear that dilatation of the narrowed segment by bougie or balloon tends to result in little or transient improvement[2,7]. Thus for patients with metastatic disease where there is no appropriate treatment for the primary disease, there seems to be no satisfactory treatment of the secondary achalasia at present.

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Heller's myotomy with partial fundoplication

P. F. Crookes, A. J. Wilkinson and G. W. Johnston

Royal Victoria Hospital, Belfast BT12 6BA, UK
Correspondence to: MR G. W. Johnston

Although achalasia is often treated by endoscopic dilatation, some patients still require a Heller's myotomy. The operation carries a low mortality and morbidity risk and the results are satisfactory in 80–90 per cent of patients. However, many operative details remain unresolved, including argument over abdominal or thoracic approach, the length of the myotomy on the oesophagus and stomach and whether or not an antireflux procedure should be added. Those who oppose the addition of an antireflux procedure claim a low incidence of gastro-oesophageal reflux following myotomy alone and point to the potentially obstructing nature of a fundoplication surrounding an aperistaltic oesophagus[1]. Other workers report a higher incidence of reflux following myotomy alone and some of these patients with reflux go on to develop oesophageal strictures[2]. In a small group of 17 patients previously treated by Heller's myotomy in our own unit, three developed oesophageal strictures out of a group of 11 patients treated by myotomy alone, whereas there were no strictures in six others in whom a full 360° wrap was added. The technical difficulty of doing a secondary fundoplication at a further operation in patients with stricture due to reflux prompted a modification to Heller's myotomy. The aim was to avoid the problem of reflux stricture on one hand and the risk of postfundoplication dysphagia secondary to a 360° wrap on the other. We report on the early results of the first seven patients treated by this method.

Patients and methods

Since May 1984, seven consecutive patients were treated for achalasia. All had typical radiological and manometric evidence of achalasia. There were five men and two women; the age range was 22–66 years. The operation was performed through the abdomen and the myotomy carried out for a distance of 5–7 cm above and 1 cm below the oesophagogastric junction. A modified fundoplication was added, in which the edges of the fundal wrap were sutured, not to each other but to the cut edges of oesophageal muscle for a distance of 2·5 cm on either side, using 2/0 interrupted linen (*Figure 1*). The cut muscle gives an excellent bite for the sutures and allows the mucosa to bulge out freely. Length of follow-up has been 1–3·5 years and included oesophageal manometry and prolonged ambulatory pH monitoring.

Results

There were no mucosal perforations. Postoperative recovery was satisfactory, and all patients were discharged by the tenth postoperative day. All patients were completely relieved of dysphagia for solids and liquids. None has developed any symptoms of reflux in the follow-up period. Pressure studies and prolonged pH monitoring are available for six of the seven patients. The other patient emigrated to Canada but reports to be free of dysphagia and heartburn. Manometry shows a small high pressure zone in the lower oesophagus in all of the six patients studied and this may represent the site of the fundoplication. The pH monitoring shows that five out of six patients are free of significant reflux. However one patient does show evidence, on pH monitoring, of nocturnal reflux with one sustained episode between 02.00 and 04.00 hours. This patient denies any symptoms of reflux on careful questioning.

Discussion

Despite the generally satisfactory results of Heller's myotomy in achalasia, most workers report a proportion of cases where dysphagia remains or returns, or where troublesome reflux develops[2–5]. In some cases this may not be related to surgical technique: operations on advanced cases with megaoesophagus do less well, carcinoma may develop, or the original diagnosis may have been incorrect. However in a substantial number of failures technical problems are responsible. Thus the oesophageal myotomy may have been inadequate in depth or length, the gastric portion of the myotomy too extensive, the cut edges may have healed in opposition, or gastro-oesophageal reflux with stricture may have occurred[6,7]. The true incidence of reflux following surgery for achalasia is unknown as not all workers specifically look for it. In particular, few studies using the sensitive method of prolonged ambulatory pH monitoring have been reported. Ellis and colleagues report significant reflux symptoms in only four of 113 patients treated by myotomy alone[8]. They attribute their low complication rate to the shortness of the myotomy on the gastric side (≤1 cm) and the minimal disruption of the diaphragmatic attachments afforded by the thoracic approach. However they do not advance data to substantiate this claim. Only 18 of their 113 patients were studied postoperatively by pH testing and eight of these patients had documented reflux. The method of pH testing is not specified. A similar claim was made in a recent review by Andreollo and Earlam[9] in which the results of more than 5000 operations were discussed. In many of the studies cited the results do not support their conclusions. Postoperative reflux was reported in 20·8 per cent[10], 35·2 per cent[11] and 23·6 per cent[12] of cases in studies where the myotomy was performed through the preferred thoracic approach. Other studies cited in this review are oversimplified; in one paper where operations were classified by the reviewer as thoracic, approximately half were done via the abdomen and the authors stated that 'there were no differences in results following either approach'[2]. The literature does not therefore support the view that optimal results are obtained by myotomy alone performed through the chest. There are further strong arguments in favour of doing an antireflux procedure as part of the original operation. For example, if reflux develops in an aperistaltic oesophagus, clearing time is much prolonged and stricture formation con-

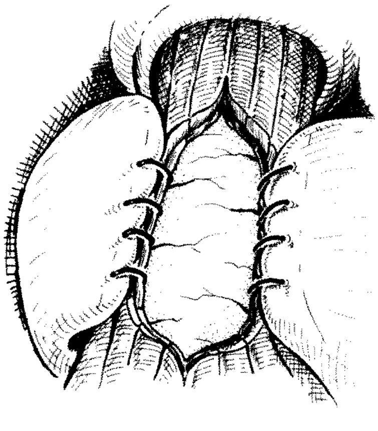

Figure 1 *Modified fundoplication*

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sequently more likely. Also, if a second operation is required, the dissection is more difficult and the risk of perforation of the unprotected mucosa is increased. Most published reports show a higher incidence of unsatisfactory results in patients requiring reoperation.

In this context, the initial results of our modified Heller's operations are encouraging, in that all seven patients are completely asymptomatic and gastro-oesophageal reflux was demonstrated in only one of six patients studied. Oesophageal manometry shows a small high pressure zone in all of six patients studied. Other workers have reported partial wrap fundoplication, but in all cases they have covered the exposed mucosa with gastric fundus[13,14]. Our procedure combines the benefits of a partial wrap fundoplication with a means of preventing reunion of the myotomy and obviates the need to excise a strip of oesophageal muscle. It is simple and avoids the necessity of thoracotomy and the not insignificant incidence of post-thoracotomy pain. To our knowledge, this technique has not been reported before.

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Paper accepted 8 August 1988

Correspondence

Angelchik prosthesis

Sir

We were very alarmed to see a report about a patient undergoing oesophagogastrectomy for the removal of an Angelchik prosthesis that had eroded into the lower oesophagus (*Br J Surg* 1988; **75**: 826).

We feel that this was an unnecessarily drastic way of treating this particular complication. We have recently had a very similar case. A 65-year-old man developed sudden onset of dysphagia 56 months after the insertion of an Angelchik prosthesis. On endoscopy the prosthesis could be seen lying in the lumen at the junction between the oesophagus and stomach. At subsequent laparotomy it was impossible to feel the Angelchik prosthesis via the abdominal approach as the prosthesis had ridden up above the diaphragm. There were marked adhesions around the lower oesophagus. A gastrotomy was made and on inserting a finger into the stomach and up into the lower oesophagus the prosthesis could be easily palpated. The prosthesis was pulled down into the abdominal cavity. A small cut down was made through the oesophageal wall on to the knot of the tapes. The tapes were thus divided and as soon as the tapes had been cut the prosthesis was easily removed. The small hole in the oesophagus was closed with interrupted silk sutures. The gastrotomy was also closed. The patient had an uneventful postoperative course, being discharged home on the fifth postoperative day. He has remained asymptomatic since. This clearly is a much simpler and safer way of removing the prosthesis and we would find it very hard to justify a resection in a benign condition.

C. M. S. Royston
J. B. J. Fozard

Hull Royal Infirmary
Hull HU3 2JZ
UK

Gallbladder non-filling at ERCP

Sir

Worthley and Toouli's finding (*Br J Surg* 1988; **75**: 796–8) that six of their eight patients with non-filling of the gallbladder at endoscopic retrograde cholangiopancreatography (ERCP) developed acute gallbladder problems after endoscopic sphincterotomy leading to death in three is of interest and concern. However, their conclusion that non-filling of the gallbladder indicates the need for cholecystectomy is contrary to the experience of ourselves[1] and others[2] who have studied many more patients. Worthley and Toouli state that our lack of effort to fill the gallbladder at ERCP limits the conclusions which can be drawn. The majority of our patients undergoing surgery after sphincterotomy had gallbladder filling at ERCP and it is difficult to understand how more strenuous efforts to fill the gallbladder on our behalf would have altered our conclusion that gallbladder non-filling is not a useful predictor of future problems.

Worthley and Toouli state that 17 of our patients required cholecystectomy for gallbladder problems. Careful reading of our paper shows that this is wrong. Eight patients underwent cholecystectomy and exploration of the common duct because of failure of endoscopic clearance not because of gallbladder symptoms. Two other patients had failed endoscopic duct clearance but were unfit for operation. Five patients underwent elective cholecystectomy after common duct clearance because their referring surgeons considered this an appropriate course of action not because of gallbladder symptoms. Only four of the remaining 65 patients required cholecystectomy for persisting symptoms and in three of these the gallbladder had filled at ERCP.

Our indications for cholecystectomy after sphincterotomy were the persistence or appearance of symptoms related to the gallbladder or failure to clear the common duct. The same criteria applied to Worthley and Toouli's study shows that, of their 12 patients in whom the gallbladder filled, two required early cholecystectomy for symptoms and two others had residual common duct stones. Thus four of 12 patients in whom the gallbladder had filled required cholecystectomy. Of their eight patients in whom the gallbladder did not fill, one had residual common duct stones and six required cholecystectomy for recurrent symptoms although one of these six patients actually required surgery for cholangitis associated with stenosis of the sphincterotomy rather than a primary gallbladder problem. Thus cholecystectomy was actually indicated in six. Worthley and Toouli have applied different criteria in their assessment of their study and ours. Applying the same criteria to both studies indicates that their data do not support their contention that gallbladder non-filling is an indication for cholecystectomy. This remains true even if we take the sensible step of excluding from analysis those patients with failed endoscopic clearance.

This matter is clearly not resolved and further long-term studies are necessary to evaluate predictors of the future development of complications. Our advice to surgical colleagues managing patients in whom they have cleared the common duct of stones but in whom the gallbladder remains in position is that acute gallbladder problems requiring surgery are not common and that elderly and high-risk patients are far more likely to die from non-biliary disease. Worthley and Toouli's paper fuels the fire for continued evaluation of these patients but has not demonstrated that patients with non-filling of the gallbladder should proceed to cholecystectomy.

D. Martin
D. E. F. Tweedle

University Hospital of South Manchester
Manchester
UK

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Authors' reply

Sir,

The number of patients in our series is relatively small when compared with other series. However, appropriate statistical analyses were applied and the differences are as reported. We have applied a Fisher's extact test after excluding those with failed endoscopic clearance and sphincterotomy stenosis as suggested by Drs Martin and Tweedle, and again show a significant difference $P < 0.05$. Therefore our conclusion remains as stated in the manuscript, i.e. 'should the gallbladder fail to opacify despite free cannulation of the common bile duct, dense opacification of the extrahepatic biliary tree and filling of the tertiary intrahepatic bile ducts, then cholecystectomy is recommended to avoid future gallbladder problems'. We are reluctant to veer from this recommendation at our institution in the light of the results which we have reported in the manuscript. The fact that some patients with a patent cystic duct also need cholecystectomy does not refute the findings of our study. However, we agree with Drs Martin and Tweedle's comments that evaluation of these patients must continue in other centres in order to either support or refute our conclusions. Our only plea is that researchers conducting these studies ensure that close follow up is undertaken in order to confirm that reported deaths from non-biliary disorders are indeed accurate. It is not uncommon for cholecystitis to aggravate cardiac disease in elderly patients leading to the cause of death being labelled as non-biliary.

J. Toouli
C. S. Worthley

Flinders Medical Centre
Bedford Park
South Australia 5042

Postoperative wound pain

Sir

We read with interest the paper by Gibbs *et al.* (*Br J Surg* 1988; **75**: 923–4) on continuous wound perfusion with bupivacaine for postoperative wound pain which reported results at variance with many published studies.

Intercostal nerve block has been found to be effective not only in producing postoperative analgesia but also in improving pulmonary function after cholecystectomy[1]. It has also been found to be beneficial after appendicectomy[2]. We have been using continuous extrapleural infusion of bupivacaine via a catheter placed at thoracotomy after thoracic and upper abdominal procedures and we have found this method to be valuable in reducing the requirement for postoperative narcotic analgesics and also in improving forced expiratory volume in 1 s (FEV_1), forced vital capacity (FEC) and peak expiratory flow rate[3].

The mechanism of action of intercostal nerve block administered extrapleurally depends not only on spread of the local anaesthetic agent longitudinally along the intercostal spaces but perhaps more importantly via paravertebral spread medially which would result in more extensive blockade[4]. This emphasizes the importance of applying the blockade at the angle of the rib concerned. Effective nerve blockade is unlikely to be achieved when the local anaesthetic agent is applied as anteriorly as that used by Gibbs *et al.* with paramedian incisions. Their results confirmed this. Furthermore, by placing the catheters between the peritoneum and the rectus muscle not only would wound infiltration be lost by leakage through the previously opened peritoneum and impeded by the rectus muscle, but also by the fact that the majority of the sensory branches of the intercostal nerves supplying the anterior abdominal wall would have become superficial to the rectus muscle at a paramedian position[5].

We believe that by modifying the technique of the infusion, the authors would have detected significant benefits from the use of continuous perfusion of bupivacaine.

J.-B. Eng
S. Sabanathan

Bradford Royal Infirmary
Bradford BD9 6RJ
UK

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'Sculpted' T tubes

Sir

In his recent correspondence, Mr Dawson (*Br J Surg* 1988; **75**: 932) describes a clinically significant bile leak following removal of a 'sculpted' T tube on the tenth postoperative day after choledocholithotomy. He concludes that the shape of the T tube is unlikely to be the critical factor for this problem.

As a proponent of the 'sculpted' T tube I have previously emphasized the need to avoid using plain or chromic cat-gut to close the common bile duct around the T tube[1]. Chromic cat-gut loses two-thirds of its tensile strength within 10–15 days, and sooner in the presence of infection which is almost invariable in choledocholithiasis. For this reason, interrupted sutures such as Vicryl® or PDS which are relatively slowly absorbed should be used.

Furthermore, after a normal postoperative T tube cholangiogram, it is useful to clamp the T tube for 24 h before actual removal. The development of symptoms following this may presage a potential leak and therefore prompt delayed removal of the T tube.

In a recent series of 223 T tubes inserted after common bile duct exploration there were five significant leaks following their removal[2]. All these had been dislodged or removed before 10 days and in no case had a 'sculpted' T tube been used; in all cases chromic cat-gut had been used to close the common bile duct. In two situations where I re-opened such patients for this problem the striking finding was a disrupted bile duct at the site of the T tube, associated with partial dissolution of the cat-gut. Using the above described techniques in my own, albeit limited, experience I have yet to experience a significant intraperitoneal bile leak.

Before accepting Mr Dawson's suggestion about the shape of the T tube as not being of major importance, can he reassure us that in the case he described he had used sutures other than cat-gut and had employed clamping before removal?

J. P. Neoptolemos

University of Birmingham
Dudley Road Hospital
Birmingham B18 7QH
UK

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Author's reply

Sir

In answer to the points raised by Mr Neoptolemos:

1. After the T tube cholangiogram was done on the seventh postoperative day, the T tube was clamped on the eighth postoperative day and remained so until the tenth postoperative day when it was removed. The patient was perfectly well during this time.
2. At operation (by me) the opening in the duct was the size of the side arm of the T tube. There was no evidence of disruption of the suture line, indeed the duct had to be incised to allow insertion of a further T tube.
3. The duct was closed with interrupted 3/0 chromic cat-gut sutures. (I use this material for biliary duct closure and anastomoses.)
4. The most significant operative finding was the total lack of any track formation around the T tube. I believe this to be the most important factor in producing this complication.

Your readers may recall that some 25 years ago plastic transparent non-irritant T tubes were introduced for a while. The incidence of biliary peritonitis following their removal was extremely high. The non-irritant plastic produced no peritoneal reaction at all.

J. L. Dawson

King's College Hospital
London SE5 9RS
UK

Diagnosis and management of graft–enteric fistulae

Sir

Dr Tilanus and colleagues (*Br J Surg* 1988; **75**: 915–6) show once again how deadly this complication can be, and that graft excision and axillofemoral bypass are not the perfect answer. For a good many years a few of us have made a plea for a more conservative approach in selected cases. In 1982[1] I published the results of direct repair in 11 of my patients, the first three of whom were operated on far away from St. Mary's by the surgeon on emergency call. It was the survival of these three, and of four others who I learned about while in New Zealand in 1975, that made me try for myself to see if such results could be reproduced. By 1982 there were eight cases, with one death from erosive gastritis, the repair being intact, two patients with early infective fistulae in whom the method was, in retrospect, inappropriate, and four patients who recovered. My second such patient, a man aged 72 years, is still alive and well 11 years after direct repair of a clean false aneurysm that was leaking into the duodenum. The fifth case was operated on by one of my ex-senior registrars; the patient re-bled fatally from an unknown source soon after the repair.

Three other patients have recovered after direct repair by my colleague Miss Averil Mansfield, FRCS. When these eleven patients were reviewed recently by Mr Michael Grigg, FRACS (unpublished results), he found that, at a mean follow-up interval of 48 months, seven were alive after simple direct suture.

I was particularly pleased that our British colleagues have published their results in the Journal, having heard their paper at an earlier stage at our Second International Vascular Symposium in London in 1986.

H. H. G. Eastcott

St. Mary's Hospital
London
UK

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Small bowel obstruction

Sir,

In regard to the case reported by Huddy and Bailey, 'Small bowel obstruction due to peritoneal encapsulation' (*Br J Surg* 1988; **75**: 262), we should like to raise some points related to the technical approach which should be kept in mind during release of such an encapsulation.

Peritoneal encapsulation, also called 'internal omphalocele'[1], is characterized by location of the small bowel behind an accessory peritoneal avascular membrane. The enclosed intestines are not necessarily normal, as stated by Huddy and Bailey, but may also be malrotated[1].

Left paraduodenal hernia is a possibility which should be considered in the differential diagnosis at laparotomy. This hernia, first described by Landzert[2] in 1871, develops in the left paraduodenal fossa and is located to the left of the fourth portion of the duodenum. It is frequently seen in the fetus and newborn and has been reported to be present in 2 per cent of autopsied bodies[3]. This fossa develops in the embryo by the elevation of a peritoneal fold by the 'vascular ring of Treitz', which is formed by the inferior mesenteric vein from above and the ascending branch of the left colic artery from below[4]. Since the 'neck' of this 'sack' contains the above-noted vascular elements, it is advisable that reduction be attempted without opening of the sack. If this is not possible the sack should be opened through its anterior wall and its contents reduced by compression from within and external traction. After reduction is completed the free edge of the sack should carefully be examined, to be divided only if no vascular structure is observed.

Otherwise, as recommended by Davis[5], the posterior peritoneum should then be incised on the left up to the duodenal–jejunal junction and the neck of the sack, containing the inferior mesenteric vein, buried in this bed, restoring its normal retroperitoneal position.

Opening of the sack by dividing the 'thickened neck', as reported by Huddy and Bailey, involves the potential risk of vascular damage and is therefore not the recommended sequence of this surgical procedure, except when the neck is clearly avascular.

Since peritoneal encapsulation and left paraduodenal hernia are both avascular membranes in a similar location, differential diagnosis should be considered. By pointing out these anatomicosurgical concepts, we hope to enhance the value of the reported case for the readers of your prestigious journal.

E. Freud
M. Zer

Beilinson Medical Center
Petah-Tikva
Israel

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Authors' reply

Sir,

Thank you for the opportunity to reply to the letter from Drs Freud and Zer. We agree entirely with the points that they make and with the necessity to distinguish between peritoneal encapsulation and left paraduodenal hernia.

The operation which they describe is a safe approach. However, in those cases where the inferior mesenteric vein can be seen not to run in the neck of the sac, division of the constricting band will allow release of the obstructed small bowel without the trauma of traction or compression. As with any surgical procedure no structure should be divided until it can be identified.

S. P. J. Huddy
M. E. Bailey

St. George's Hospital Medical School
University of London
UK

'Loop mattress suture'

Sir

The mattress suture, which has a deep bite, is useful for the elimination of dead space under a wound and provides excellent apposition of the edges of the wound. We have successfully used this method of stitching mattress sutures in many types of plastic reconstructive surgery during the past 10 years. Dr Condon described his method in 1968, and Dr Gault reported a similar method in 1987 within the pages of this Journal. In each case, removal of stitches is accomplished by incising the loop of the knot.

In our method (*Figure 1a*), we feature a long loop which is easily severed, enabling smooth removal of the suture by applying slight traction. In Gault's method (*Figure 1b*), there is the possibility of a suture being severed at a point other than the quite short loop, thereby hampering easy removal of a suture.

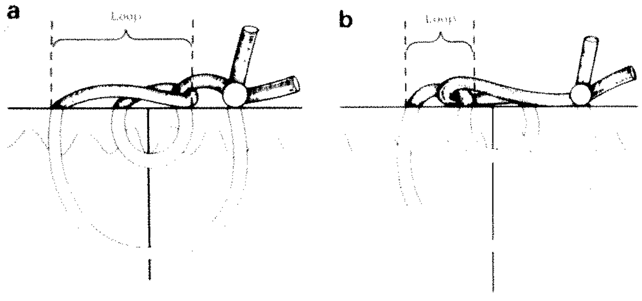

Figure 1 *The length of the loop* **a** *in our method, as compared with* **b** *Dr Gault's method*

Y. Bandoh

Juntendo University
Tokyo
Japan

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Review of a hospital experience of breast abscesses

Sir

We would like to add our experience to that of P. K. H. Tam and H. Brooks (*Br J Surg* 1988; **75**: 190) who make a plea for the treatment of breast abscesses by needle aspiration as an alternative to incision and drainage.

The original article by J. H. Scholefield, J. L. Duncan and K. Rogers[1] (*Br J Surg* 1987; **74**: 469–70) pointed out that the majority of such abscesses in practice today are due to duct ectasia, and the infective organisms, if any, are anaerobic.

At our breast clinic we have seen a large number of such cases and it is our practice to treat them by needle aspiration and bacteriological examination, followed by suitable antibiotic therapy. In many the 'abscess' is a sterile inflammatory reaction to the inspissated material in the ducts which has leaked into periductal tissue. Breast ultrasound has shown itself to be a very useful way of confirming diagnosis, and surgical incision has not been necessary.

We would agree with Scholefield, Duncan and Rogers that if any surgical treatment is necessary, a major excision of the duct system (Hadfield's operation) is the treatment of choice. It is much better, however, to carry out this procedure when any sepsis has resolved.

The surgical scarring which is produced by conventional incision and drainage of breast abscesses is very unsightly and in our opinion unnecessary in most cases.

A. G. Nash
T. Powles*

St. Helier Hospital
Carshalton
**Royal Marsden Hospital*
Sutton
UK

Femorodistal graft stenoses

Sir,

We read with interest the paper by Grigg *et al.* on femorodistal graft stenoses (*Br J Surg* 1988; **75**: 737–40). Our experience with Duplex scanning has been similar[1,2]. We would certainly agree that measurements of flow rates show a great deal of variation and have limited application in graft surveillance[3].

One of the repeated criticisms we have faced in the past is that scanning a whole graft must be a lengthy procedure. With experience we have found this not to be the case and new developments, e.g. colour coded Doppler flow, make more rapid scanning feasible. As Grigg *et al.* suggest a 6-weekly surveillance in the first 6 months we are sure they agree with us on this point. The distal anastomosis can be difficult to assess in femoropopliteal grafts. Where the distal anastomosis is to a crural vessel, then assessment is much easier. It would be interesting to know the difficulties Grigg *et al.* experienced with this technique. We feel it is also worth pointing out that Duplex scanning can be used to assess all types of grafts as others have found[4].

We would also support the suggestion that thrombogenicity must be a source of some graft failures. In our prospective study five out of six grafts which occluded without warning were prosthetic.

Documenting these facts objectively and non-invasively will increase our understanding of the causes of graft failure and help prevent it.

This important paper adds to our own reports on the usefulness of Duplex scanning in graft assessment and provides a simple objective criterion for categorizing graft stenoses which we shall certainly adopt.

M. D. McShane
A. D. B. Chant

Royal South Hants
Southampton
UK

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Author's reply

Sir

McShane and Chant are generous in their comments on our paper and we are grateful. Many units in both Europe and the USA have used Duplex for graft follow-up with varying success. Firstly, the technique can be time consuming and we agree that technical developments have improved this, but it remains imperative to assess the whole graft rather than sampling it, as velocities and flow may return to normal downstream from a stenosis. Secondly, as they point out, the distal anastomosis can be difficult to assess. We sought to overcome this problem by assessing the graft just proximal to the anastomosis and the popliteal artery just distal to it. This problem only arises in femoropopliteal grafts as anastomoses to crural vessels at the level of the ankle are easier to assess. However, in these patients the small distal vessels may be difficult to pick up.

Many aspects in the postoperative use of Duplex scanning were not mentioned in our paper, and we apologize if this confused the reader. The single purpose of our communication was to publish a reproducible formula that should simplify our objective assessment—particularly in the assessment of early, non-haemodynamically significant stenoses.

J. H. N. Wolfe

St. Mary's Hospital
London W2 1NY
UK

Body wall ecchymosis

Sir,

We read with interest the paper by Wilson on body wall ecchymosis in acute pancreatitis (*Br J Surg* 1988; **75**: 704). We would like to draw attention to another previously unreported differential diagnosis of abnormal wall bruising.

Case report

A 58-year-old man presented with a 2-day history of vomiting, crampy colicky abdominal pain and constipation. There was no previous history of abdominal surgery. On examination there was an area of discoloration periumbilically. Apart from a possible paraumbilical mass with a cough impulse no other physical signs were elicited.

At operation, a periumbilical hernia with a small neck of viable small intestine and strangulated fat was found. The fat and hernial sac were excised, the peritoneum was closed and the defect repaired. The patient made an uneventful recovery.

Cullen's sign was originally described as a feature of acute haemorrhagic pancreatitis (Grey Turner's sign is discoloration in the flanks, whilst Cullen's sign is in the anterior abdomen). Cullen-like coloration has been reported in ruptured abdominal aortic aneurysm, ruptured ectopic pregnancy and mesenteric infarction. The present case illustrates this sign in strangulated paraumbilical hernia. The mechanism is uncertain but may involve necrosis of tissue producing local skin inflammation. Awareness of this sign may help in the differential diagnosis of all the above conditions.

A. K. Banerjee
M. Burke

Northwick Park Hospital
Harrow HA1 EUJ
UK

Incisional hernias

Sir,

In the surgical workshop section (*Br J Surg* 1988; **75**: 689) an operation is described for incisional hernia. It is unattributed and unreferenced suggesting that it is a novel concept and technique which it is not. Ton[1] in 1967, Boerema[2] in 1971 and subsequently others[3] have described in full the concept and detailed description of this operation. The definition of patients who are suitable is not discussed; small and moderate incisional hernias do not require this operation, only those which are 10 cm or more in diameter. The notion expressed that only those who have dieted successfully should be considered denies the realities of the clinical situation. These large incapacitating hernias often occur in exactly the obese middle aged patients who are quite unable to reduce weight by any means as their energy expenditure is so limited by pain and hernial size. The technique described leaves much to be criticized: the peritoneum, contrary to the advice given, must be opened to free large areas of omental attachments; the use of material as pliable as Redivac® drains (O.E.C. Orthopaedic) (even 'large') is inadvisable; 6 mm Teflon® (Du Pont, UK) rods with predrilled holes every 2 cm are far preferable. The emergence of these tubes from the skin exposes the patient to the risk of infection. In a series of 38 Boerema type repairs done by ourselves and Mr A. B. Birt and colleagues from Norfolk, wound infection was the most serious complication despite complete skin coverage and antibiotic prophylaxis. Certainly the use of nylon does not 'eliminate' infection.

This description is imprecise, wrong in important details, lacking in long-term follow up in any significant numbers and inadequate in its indications.

A. E. Kark

The Clementine Churchill Hospital
Harrow HA1 3RX
UK

1. Ton JG. Tijdelijke prosthesen bij het sluiten van geinfecteerde Littekenbreuken. *Nederlands Tijdschrift voor Geneeskunde* 1967; **111**: 972–3.
2. Boerema I. Cause and repair of large incisional hernias. *Surgery* 1971; **69**: 111–16.
3. Doeven JJ. Results of treatment of incisional hernias with extractable prostheses. *Archivum Chirurgicum Neerlandicum* 1975; **27**: 245–55.

Parotid tumours

Sir

Mr Maynard draws attention to an important point in the diagnosis and misdiagnosis of parotid tumours in his article (*Br J Surg* 1988; **75**: 764–6). There is substantial documentation that the treatment of choice with the lowest recurrence rate for pleomorphic adenomas is complete extracapsular excision after exposure of the facial nerve trunk and branches. However, in dealing with benign parotid tumours such as adenolymphoma, and especially enlarged lymph nodes, enucleation is an appropriate treatment.

We have previously reported[1] the need for the precise diagnosis of the nature of parotid tumours to avoid just the problem which Mr Maynard raises. In all masses in the lateral neck in the vicinity of the parotid and especially in those laying beneath the angle of the jaw in the situation commonly occupied by enlarged jugulodigastric lymph nodes, two investigations will provide certain diagnosis in virtually every case. Firstly, a fine needle aspiration biopsy will identify pleomorphic adenoma in 100 per cent of cases and adenolymphoma in 60–70 per cent[1,2]. Secondly, CT scan will demonstrate the parotid gland and the position of the occupying tumour with precision. In the event of an outlying or separated tumour mass, the fine needle method will have established its nature.

The use of these tests will help reduce or eliminate the problem of inadequate parotid tumour operations on the one hand and on the other permit less hazardous enucleation for those masses which only need this form of removal.

E. R. T. C. Owen
A. E. Kark

Northwick Park Hospital
Middlesex HA1 3UJ
UK

1. Owen ERTC, Prichard AJN, Hudson EA, Kark AE. Accurate pre-operative diagnosis of parotid swellings by fine needle aspiration cytology and computerized tomography scanning. *Br J Surg* 1986; **73**: 1035.
2. Ebbs SR, Webb AJ. Adenolymphoma of the parotid: aetiology, diagnosis and treatment. *Br J Surg* 1986; **73**: 627–30.

Book reviews

A Colour Atlas of AIDS and HIV Disease

C. F. Farthing, S. E. Brown, R. C. D. Staughton. Pp. 113. Illustrated. 1988. London: Wolfe Medical Publications. £16.00.

I have found this a most informative book. The book first reviews the history and epidemiology of the AIDS epidemic. The virology and immunology are next described, and antibody tests and the clinical response to HIV are explained. These explanations are particularly recommended as they are lucid and comprehensive.

The clinical manifestations of AIDS are well illustrated by colour photographs and there is a most useful chapter on counselling.

This book can be confidently recommended to the practising doctor, be he in hospital or community practice. The book is coherent and comprehensive, well illustrated and without typographical or other editorial mistakes.

H. B. Devlin

Consultant Surgeon
North Tees General Hospital
Stockton-on-Tees
UK

Laparoscopy

J. W. Saleh. 178 × 267 mm. Pp. 265. Illustrated. 1988. Philadelphia: W. B. Saunders. £44.00.

It is difficult to be sure for whom this book is intended. The title suggests that all aspects of laparoscopy will be discussed fully but gynaecologists and general surgeons are likely to be disappointed for the author's declared interest in hepatology makes this effectively a textbook of medicine. Only two chapters deal with emergency and gynaecological laparoscopy.

Although well written and presented, not enough space is allowed to explore the more challenging use of the laparoscope in the acute abdomen. There is no mention of the 4 mm mini-laparoscope recently developed by Stortz for use in blunt injuries of the abdomen. Also, sadly, not enough is made of the value of laparoscopy in the differential diagnosis of lower abdominal pain, particularly that between appendicitis and gynaecological causes of pain where inappropriate surgery may have an adverse effect on the reproductive potential of the young woman treated.

The emphasis on a local rather than a general anaesthetic approach again displays the author's medical background, but a hint of the therapeutic value of laparoscopy in the hands of the physician is well described in the division of adhesions, particularly in the Fitz-Hugh–Curtis syndrome — a condition undergoing a revival at the present time. The technical aspects of laparoscopy are well described with excellent line drawings and colour photographs. The section on gynaecological laparoscopy is particularly good, giving some idea of the potential of this instrument in surgery in the future.

Despite a seemingly critical review this is a very readable book but, for the surgeon, it will inevitably remain a reference book only.

B. F. Ribeiro

Consultant Surgeon
Orsett Hospital
Grays
UK

Atlas of General Thoracic Surgery

M. M. Ravitch. 218 × 282 mm. Pp. 413. Illustrated. 1988. London: Academic Press. £77.95.

The authors are internationally known thoracic surgeons. As they readily accept, the book owes much to the work of an outstanding medical illustrator and it is perhaps a little surprising that he is not included as an author. The book is 413 pages long and contains a comprehensive index. There are nine sections covering anatomy, chest wall operations, the diaphragm, thoracic incisions, the thoracic skeleton, diagnostic and therapeutic procedures, pulmonary resections, trachea and oesophagus. Most sections cover several operations and alternatives are proposed. The choice of operations is comprehensive. Over 30 excellent coloured plates are used to illustrate normal anatomy in several sections of the book. Over 100 operations and procedures are described with line drawings and black-and-white shaded plates. Each procedure is accompanied by a small number of key references. As acknowledged by the authors, many of the drawings have already been used elsewhere. Whilst this is reasonable economy, these are often combined with line drawings which are sketchy and the lack of uniformity within a subject leads to confusion. Some of the line drawings are complex and colour would have been preferable. The section on the chest wall is perhaps too extensive, being 77 pages in length, but this is understandable given the special interest in this subject by some of the authors. The section on thoracic incisions inevitably displays an individual approach and, whilst one must respect the experience of the authors, most thoracic surgeons in this country would not now resect the back-end of the ribs in an uncomplicated thoracotomy. The section on diagnostic procedures covers simple undertakings such as needle biopsy and intercostal drainage. The section on mediastinoscopy is not well illustrated and colour would have been preferable. One must take issue with the routine resection of costal cartilage when undertaking anterior median sternotomy. The sections on pulmonary resection and oesophageal disease are thorough but throughout there seems to be an undue emphasis on stapling techniques. Surely, even in the United States there are surgeons who still prefer suture techniques and I found this overemphasis irritating. The section on the trachea is written by Dr Grillo, a renowned expert in this field. Unfortunately too few illustrations are used and these complex operations are therefore understandable only to those experienced in this specialized field.

It is difficult to appreciate the market intended for this book. It is perhaps a tribute to the illustrator that some of the operations are made to look easy, especially those in pulmonary resection. Many of the key early steps in such operations are omitted and the illustrations may encourage the inexperienced to attempt surgery which would be beyond their ability. This book is very definitely for the experienced thoracic surgeon or those advanced in their training, and therefore the inclusion of intercostal drainage and thoracic incisions would appear unnecessary. This book provides no substitute for formal training and apprenticeship but is an excellent supplement and will find its way deservedly into the reference libraries of those institutions concerned with thoracic training.

P. Goldstraw

Consultant Cardio-thoracic Surgeon
The Middlesex Hospital
London W1N 8AA
UK

Otolaryngology: Head and Neck Surgery

D. D. Weese, W. H. Saunders, A. J. Schleuning. 267 × 168 mm. Pp. 600. Illustrated. 1988. St. Louis, Missouri: C. V. Mosby Co.

This seventh edition of a standard North American text is aimed primarily at resident training programmes but also at medical students, nurses and dentists. The authors have attempted to encompass the whole of the speciality of otolaryngology, head and neck surgery, including audiology, reconstructive and facial cosmetic surgery, into one volume of just under 600 pages. The use of a rather long-winded discoursive style has made this objective almost unattainable. Although the management of the various regions such as the larynx and hypopharynx follows a set pattern with anatomical descriptions followed by physiology and embryology, the constraints of space have made it impossible to present, for example, physiology in an adequate way which might satisfy the examiners in the Board examinations or The Royal College of Surgeons. Although several of the chapters are excellent and cover the field adequately — particularly salivary gland disease and dizziness and vertigo — I am afraid that there is a lack of direction and commitment in several others. The chapter on sinus disease omits any mention of sinoscopy or functional endoscopic surgery and the discussion of sinus malignancies is incomplete and misses out the ethmoid sinuses and developments in cranial facial surgery completely.

Although this book is nicely produced and well illustrated, as it stands it would not provide an adequate fund of knowledge to ensure a pass in the specialist examinations in the UK.

C. B. Croft

Consultant ENT Surgeon
The Royal National Throat, Nose and Ear Hospital
London
UK

Notices and announcements

21–22 January 1989
Hong Kong Surgical Forum
University of Hong Kong, Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

25–26 January 1989
Thrombolysis: The Dawn of a New Era?
U.K.
Information: Penny Robinson, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK

12–18 February 1989
Diabetic Control and Complications: An Interactive Workshop
London, UK
Information: Director, Courses Department, 65 Davies Street, London W1Y 2AA

19–22 February 1989
3rd United Arab Emirates Cancer Conference
Dubai, United Arab Emirates
Information: Conference Secretariat, 3rd U.A.E. Cancer Conference, Emirates Medical Association, P.O. Box 6600, Dubai, United Arab Emirates

19–23 February 1989
7th Congress of the Association of Surgeons of South East Asia
Penang, Malaysia
Information: Congress Secretariat, 7th Congress Ssian Surgical Association, c/o Tawakal Specialist Centre, 198A-208A Jalan Pahang, 53000 Kuala Lumpur, Malaysia

19–24 February 1989
Diagnostic Imaging Update
Park City, Utah, USA
Information: Radiology Postgraduate Education, Room C324, University of California, San Francisco, California 94143-0628, USA

24 February 1989
Femoro-popliteal Bypass: Can Better Assessment Lead to Improved Results?
Leicester, UK
Information: Miss Rosalind Aldwinckle, Secretary to Professor P. R. Bell, University of Leicester School of Medicine, Department of Surgery, Clinical Sciences Building, The Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, UK

25–26 February 1989
Second Annual Congress on the North American Society of Phlebology
New Orleans, USA
Information: Pat Curl, Course Coordinator, North American Society of Phlebology, 3960 Park Boulevard, Suite E, San Diego, California 92103, USA

4–11 March 1989
7th Winter Congress: Diagnostic Imaging
Courchevelle, France
Information: Ms Mary Ullman, Winter Congress, 21915 Roscoe Boulevard, Suite 222, Canoga Park, California 91304, USA

5–7 March 1989
Surgical Masterclass for Consultants and Senior Registrars in General Surgery
Aviemore, U.K.
Information: Clerk to the College, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

5–10 March 1989
Magnetic Resonance Imaging Update 1989: Winter Conference
Snowbird, Utah, USA
Information: Radiology Postgraduate Education, Room C324, University of California, San Francisco, California 94143-0628, USA

12–15 March 1989
Current Problems in Breast Cancer
Vienna, Austria
Information: Secretariat ICS, Elisabeth Ribar-Maurer, c/o Wiener Medizinische Akademie, Alser Strasse 4, A 1090 Vienna, Austria

27–31 March 1989
Neuroradiology at Vail
Vail, Colorado, USA
Information: Janice Ford or Nancy Fedullo, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA

29–31 March 1989
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information: The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

6–9 April 1989
4th ASEAN Otorhinolaryngological Head and Neck Congress
Singapore
Information: Dr R. E. Stanley, Organizing Secretary, c/o ENT Department, Singapore General Hospital, Singapore 0316

12–14 April 1989
VIth International Conference: Polymers in Medicine and Surgery
Leeuwenhorst Congress Centre, The Netherlands
Information: Joanna Evans-Thomas, Conference Officer, The Plastics and Rubber Institute, 11 Hobart Place, London SW1W 0HL, UK

4–17 June 1989
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information: Dr J. F. Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 13214, USA

21–23 June 1989
71st Annual Meeting of The Endocrine Society
Seattle, Washington, USA
Information: The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

24–27 June 1989, 28–30 June 1989
Second Mediterranean Surgical Congress
Athens, and continued in Heraklion, Crete, Greece
Information: Ms Peggy Alexopoulou, Public Relations Centre, 56 Hippocratous Street, 106 80 Athens, Greece

2–15 July 1989
Neonatal and Paediatric Surgery
Manchester, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

15–16 July 1989
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27 August–1 September 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Information: International Congress and Convention Association, PO Box 50006, Tel Aviv 61500, Israel

6–8 September 1989
Fourth World Congress of the International Society for Diseases of the Oesophagus
Chicago, Illinois, USA
Information: 4th World Congress of the International Society of Diseases of the Oesophagus, 911 Busse Highway, Park Ridge, Illinois 60068, USA

10–15 September 1989
3rd International Symposium on Inflammatory Bowel Diseases
Jerusalem, Israel
Information: International Congress and Convention Association, P.O. Box 50006, Tel Aviv 61500, Israel

21–23 September 1989
Annual General Meeting of the Association of Surgeons in Training
Cardiff, Wales, UK
Information: Mr Taylor, Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

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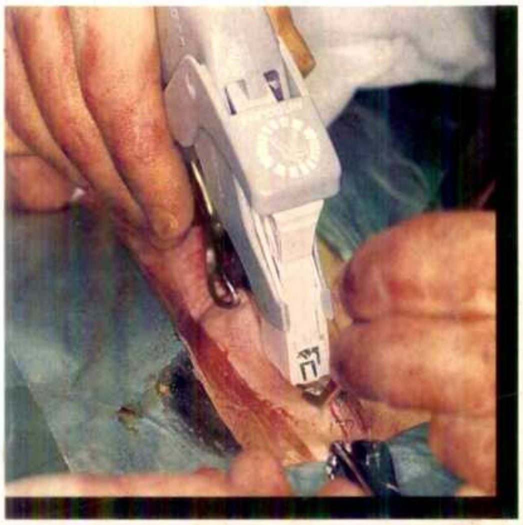
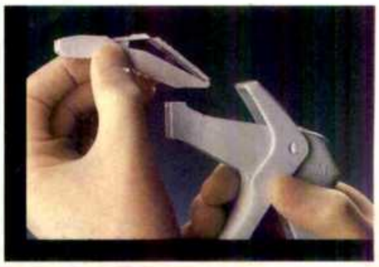
The 'Precise' skin stapling system



Each **Precise** stapler can be loaded, magazine style, into a handle.



Stapling is four times faster than skin suturing.[1] Patients spend upto 33 minutes less on the operation table.[2] Poor risk patients can spend less time under anaesthetic.[2,3,4] Better cosmetic results and lower infection rates are possible.[5,6] **Precise** skin staplers have been shown to be cost effective.[1]

Precise skin staplers operate in one smooth, fast action.

Significant savings include:

Freeing of theatre time.[2]
Conservance of expensive anaesthetic agents.
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More efficient use of beds for in-patient cases.
These are compelling reasons for choosing **Precise** skin staplers.

References:

1 George, T.K. and Simpson, D.C. (1985) Skin wound closure with staples in the Accident and Emergency Department. Journal of the Royal College of Surgeons of Edinburgh, **Vol 30,** No. 1, 54–56.

2 Pritchard B. and Pritchard, C. (1985) Skin staples, NATNews, July.

3 Traub, A.C. and Quattlebaum, F.W. (1981) Cutaneous Wound Closure: Early Staple Removal and Replacement by Skin Tapes. Contemporary Surgery, **Vol 18.**

4 Jewell, M.L., Sato, R. and Rahija, R. (1983) A Comparison of Wound Healing in Wounds Closed with Staples Versus Skin Suture. Contemporary Surgery, **Vol 22,** 29-32.

2 Bucknall, T.E. and Ellis, H. (1982) Skin Closure. Comparison of Nylon, Polyglycolic Acid and Staples. Euro. Surg. Res., **14,** 96-97.

6 Pickford, I.R., Bennan, S.S., Evans, M. and Pollock, A.V. (1983) British Journal of Surgery, **70,** 226.

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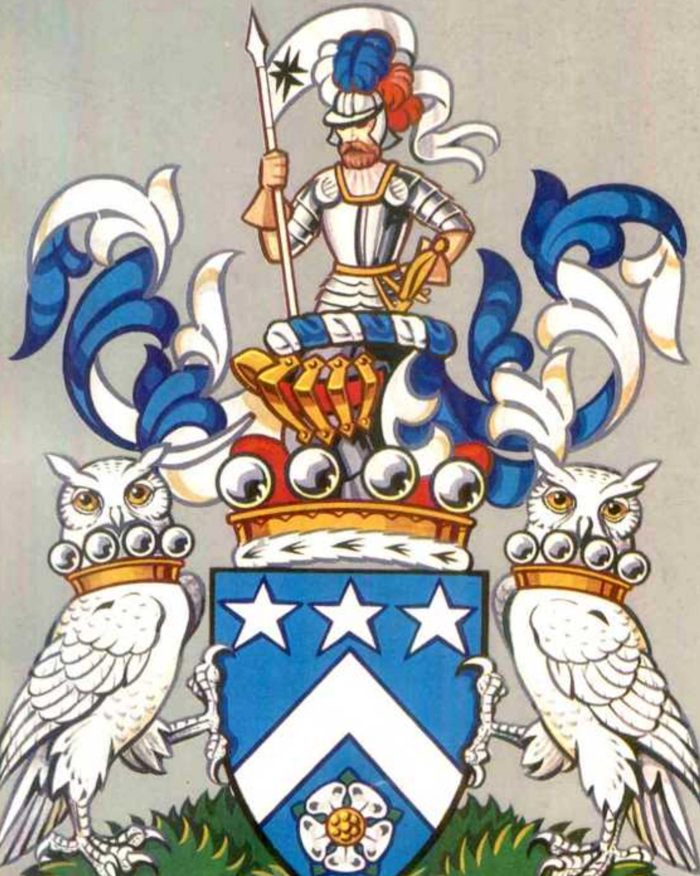
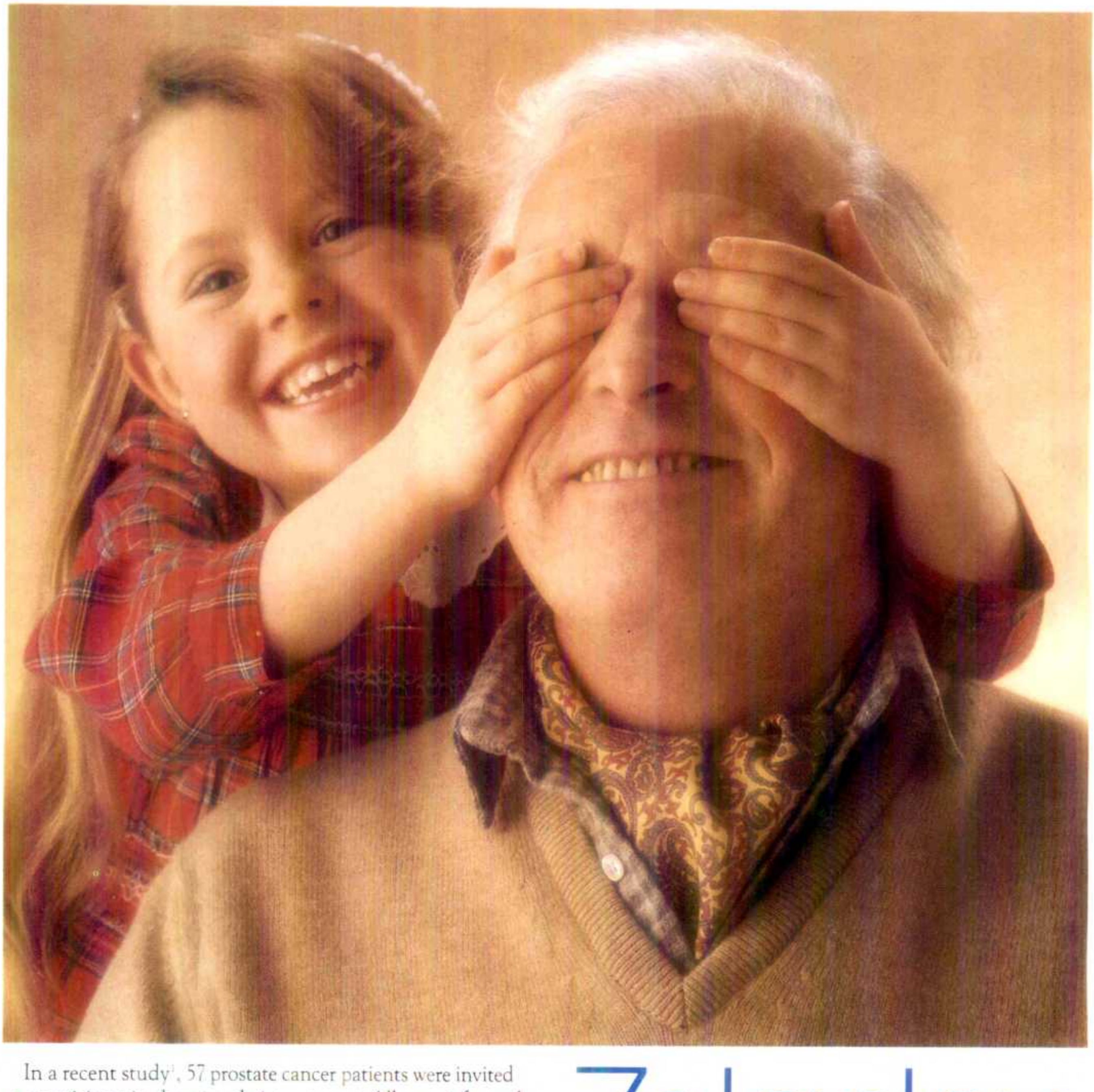
The British Journal of Surgery

Volume 76, Number 2, February 1989



Guess which prostate cancer treatment most patients would choose.



In a recent study[1], 57 prostate cancer patients were invited to participate in choosing their treatment. All were informed that the two treatments available, sub-capsular orchidectomy or 'Zoladex', were similar in efficacy and side effects. 49 of the patients (86%) opted for 'Zoladex'.

A recent trial[2] has established the equivalence of 'Zoladex' to orchidectomy.

Zoladex

goserelin

Effective therapy without surgery.

▼ 'ZOLADEX' PRESCRIBING NOTES.

Use: Prostate cancer suitable for hormonal manipulation. **Presentation:** A sterile depot containing goserelin 3.6mg. **Dosage and administration:** One depot injected subcutaneously into the anterior abdominal wall every 28 days. **Precautions:** Care with patients at particular risk of developing ureteric obstruction or spinal cord compression. Consider initial use of an anti-androgen at the start of therapy. **Side effects:** Hot flushes, decrease in libido and occasional breast swelling and tenderness. Skin rashes (generally mild). Occasional mild bruising at injection site. Initial transient increase in serum testosterone may cause temporary increase in bone pain. **Product licence number:** 29/0198. **Basic NHS Price:** £114.00 per depot. 'Zoladex' is a trademark. Further information is available from: ICI Pharmaceuticals (UK), Southbank, Alderley Park, Macclesfield, Cheshire SK10 4TF.

Reference 1. Lunglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex'– a new treatment for prostatic cancer. International Congress and Symposium Series.* 125. London: RSM Series, 1987: 47-51.
2. Peeling W B. ibid: 27-46.

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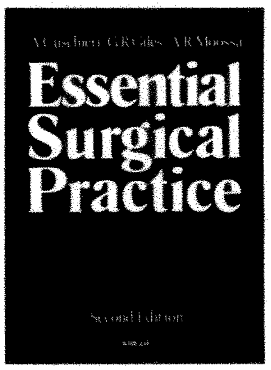

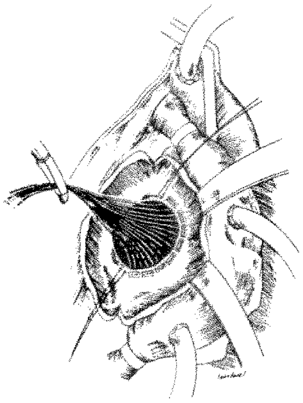

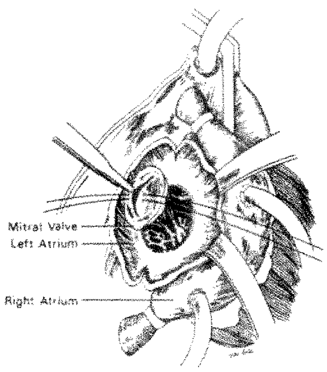

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In order to fulfil the functions and duties of such an Association it would be necessary for the Section to cater more widely for proctologists who do not find it easy to travel to London. To meet this need it is hoped to set up a series of Regional "Chapters" based upon existing coloproctology societies and groups and providing representation for such groups on the Council. It is also hoped to build on the Section's current policy of holding out of town meetings in regional centres in Scotland, Wales, the North of England and Northern Ireland.

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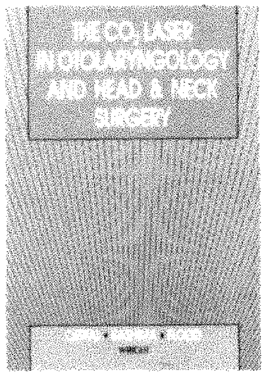

Editors:

V H Oswal FRCS, DLO
Consultant ENT Surgeon, North Riding Infirmary, Middlesbrough, Cleveland, UK

H K Kashima MD
Professsor, Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA

L M Flood FRCS
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Br. J. Surg. 1989, Vol. 76, February, 107–108

A new solution for liver preservation

It is now 25 years since the first human orthotopic liver transplant was performed by Dr Thomas Starzl in Denver and 20 years since the first such procedure was performed by Sir Roy Calne in Cambridge. The intervening years have seen many advances in patient management and immunosuppression with steadily improving results. The 1983 NIH Consensus Conference concluded that 'liver transplantation is a therapeutic modality for endstage liver disease that deserves broader application'[1] and in recent years there has been a rapid increase in both the number of units undertaking liver transplantation and the number of patients receiving such grants.

One of the areas of deficiency identified in the consensus report was in preservation of the liver before transplantation. In the early days of liver grafting the donor organs were all retrieved following hypoxic cardiac arrest after discontinuing ventilation. To minimize the additional ischaemic insult of added storage time for transportation it was the practice to use only donors in the same hospital or occasionally, as in Sir Roy Calne's early cases, to transport the recipient and a full support team to the donor hospital[2].

The work of Collins *et al.*[3] on the kidney and Schalm *et al.*[4] on the liver added the concept that a solution might be used to supplement the effect of core cooling and hypothermia, allowing longer preservation periods. These solutions were rapidly taken into clinical practice, the Cambridge group using a modified version of Schalm's solution[5] and most others adopting Collins' solution. In this way distant procurement of livers became possible[5] and acceptance of the concept of brain stem death[6] and the 'heart beating donor' allowed the removal of organs in optimal condition. Preservation times could then be safely extended to 6–8 h and in some cases even to 12–14 h. In the human kidney, storage periods of 24–30 h are routine using simple cold storage techniques and the failure to achieve similar storage times in the case of the liver was attributed to the metabolic complexity of the hepatocyte rather than to any deficiency in the storage solution. Experimentally, longer preservation times were achieved using machine perfusion or combinations of drugs with modified storage solutions but these techniques proved too complex to gain widespread acceptance.

The major factor in organ preservation is hypothermia. This reduces the cell's metabolic requirements and prolongs the period it is able to survive under anoxic conditions. However, hypothermia also disrupts the cell's normal homoeostatic mechanisms and the loss of the cellular mechanism for volume regulation is thought to be particularly damaging. Most organ preservation solutions contain impermeant substances such as glucose, mannitol and citrate which remain in the extracellular space and thus osmotically inhibit hypothermic cell swelling. The hepatocyte, however, is freely permeable to many such agents, offering a possible explanation for the failure of these solutions in the liver. In 1986 Wahlberg *et al.* described a preservation solution for the pancreas based on the trisaccharide raffinose and the lactobionate anion[7]. In their initial tissue slice studies the raffinose and lactobionate combination was also shown to be effective in suppressing cell swelling in hepatocytes. It thus appeared potentially useful for liver preservation and this was confirmed in 1987 by a member of the Cambridge group working in the same laboratory in the University of Wisconsin in Madison[8]. Dog livers were successfully transplanted after 24–48 h cold storage using Wahlberg's original formulation but omitting dexamethasone, or using a simplified variant also omitting hydroxyethyl starch and adenosine. The original solution[7], now known as UW solution, has since entered widespread clinical use in trials in both the USA and Europe with livers being stored for more than 24 h on several occasions.

The implications of this new solution are considerable. In Cambridge we have used a simplified variant in over 60 liver transplants with preservation times of up to 17 h, allowing operations to be performed as 'semi-elective' procedures during daylight hours with full support services readily available. In the case of unanticipated difficulty in the recipient hepatectomy the dissection can be carried out slowly and carefully without fear of compromising the graft due to the lengthening preservation time. Transport and sharing of precious organs for transplantation is possible over even greater distances and the difficult logistical tasks involved in co-ordinating donor and recipient procedures have been simplified. Already a liver has been transported from North America on a scheduled commercial flight and transplanted in Paris. The

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solution is highly effective in preservation of the pancreas and the kidney. Its application in transplantation of these organs is undergoing clinical trials and early experimental results suggest that it will also prove effective in heart preservation.

The importance of this solution lies not only in its effect on liver transplantation but, more importantly, in its effect in restoring enthusiasm and interest in the field of organ preservation, a field which for many years has attracted little interest in the absence of any apparent clinically applicable progress. It is already clear that the new solution is over-complex, containing as it does many components included for purely theoretical reasons or incorporated from machine perfusion practice but not necessarily needed in cold storage[10]. I feel sure that the coming years will see many more new and effective solutions being produced to the benefit of transplant surgeons, who will be able to spend their nights in bed rather than in the operating theatre, and of their patients who will receive a better preserved organ under the best conditions possible to ensure success.

N. V. Jamieson

Cambridge University Department of Surgery
Addenbrooke's Hospital
Cambridge

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Cryptorchidism

In 1762 John Hunter concluded that the testicle was directed in its descent by the gubernaculum—the word meaning 'helm', or 'helmsman'—and, if descent were arrested, he said '... it is not easy to ascertain the cause of failure of descent, but I am inclined to suspect the fault originates in the testicles themselves'. Some 200 years and many written words later it is still 'difficult to ascertain'. The condition is known to be commoner in boys whose mothers have been exposed to exogenous oestrogens during pregnancy. The source of the oestrogen is, in some instances, a pregnancy test and, in others, perhaps the unwitting continuation of the contraceptive pill during early pregnancy. There is also an increased incidence in the offspring of obese mothers and in first born boys, and there is an unexplained seasonal variation. The apparent importance of hormonal factors in testicular descent has stimulated a great deal of research, some directed at producing 'medical' as opposed to 'surgical' treatment. The latest, an investigation into the use of luteinizing hormone releasing hormone, has proved disappointing. Although luteinizing hormone is easier to administer in a nasal spray, there appear to be few significant advantages over the previously used human chorionic gonadotrophin. No testis which is impalpable can be encouraged to descend, and there is still the suspicion that the testis which does would have done so anyway at, or before, puberty.

The descent of the testis from its original site on the posterior abdominal wall has been described in two phases: firstly, intra-abdominal descent and, secondly, after the 28th week of gestation, that in which the testis enters the inguinal canal to emerge from it to pass into the scrotum, between the 34th and 40th week. It follows that in babies born prematurely, and many more such babies are surviving, there will be a higher incidence of cryptorchidism. Although the mechanism of descent is not fully understood, the factors influencing the first phase include differential growth of the fetus in relation to the position of the developing testis and possibly changes in the pressure of the coelomic fluid. The gubernaculum plays an important part in the second, or true phase of descent, although by what means is not yet clear. Indeed, there is not even universal agreement about its morphological structure.

Terminology

Although testicular position can most easily be defined as normal or abnormal, one of the problems besetting the subject has been terminology. Terms such as 'imperfectly descended', 'undescended', and 'maldescended', have been commonly used, sometimes to describe the same condition. The term cryptorchidism has come into wider use in recent years and although literally meaning 'hidden testis' (Greek: *cryptos*: *orchis*), it is reasonable to accept it as describing any abnormally positioned testis.

The normal testis includes the scrotal testis and the retractile testis. After the neonatal period the scrotal testis may be drawn up by the cremasteric muscle to a high scrotal or an inguinal position. In the inguinal position it is held in the superficial inguinal pouch which is slightly lateral and superior to the external inguinal ring. The cremasteric reflex is not present in the newborn and so it is important that as part of the immediate postnatal examination by paediatrician or midwife, the testicular position is recorded. For practical purposes, the testis which has been accurately recorded as in the scrotum at birth and which in later years is found to be higher in position, is a normal retractile testis. Differentiation between a testis which is inguinal or high scrotal and retractile, and a testis which is in the same position but held there abnormally and has never been low in the scrotum, may be most difficult without the neonatal record. In one instance the testis is normal, in the other abnormal.

The abnormal testis is never low in the scrotum and cannot be manipulated into this position. It may be held up on the normal track (the imperfectly descended testis) where it is palpable if it lies outside the external ring, and impalpable if it lies within the inguinal canal (the canalicular testis) or the abdominal cavity. The abnormal testis may also, rarely, be palpable in one of the subcutaneous ectopic positions (the maldescended testis), for example, perineal or femoral. The clue to diagnosing an ectopic testis may be the presence of a palpable spermatic cord at the external inguinal ring, so leading the examiner to the misplaced testis. Palpation for the cord at this site, which may be quite difficult in a podgy infant, is an essential part of clinical examination for, if

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present, it will also raise the question whether the testis has atrophied (the vanishing testis). Such atrophy, which is a commoner finding than ectopia, occurs following pre-, peri- or unrecognized postnatal torsion, or after vascular injury during herniotomy or orchidopexy.

Two further points regarding the nomenclature and clinical examination must be made. The abnormal testis may be held up in the superficial inguinal pouch, owing to abnormal gubernacular attachments in this region, or to a fascial barrier preventing its access to the scrotum, or both. It has been classified as an 'inguinal ectopic testis', although it lies in a pouch in which the normal testis may be found. It would be better, perhaps, if this abnormality were referred to, as some have in the past, as the 'obstructed' testis. It is not an uncommon cause of cryptorchidism and its differentiation from a retractile testis in an anxious boy with a well developed cremasteric reflex may tax even the most experienced. The second, and less common problem, has been recognized only in recent years. It had always been assumed that a boy diagnosed as having a rectractile testis would, at puberty (when the cremasteric reflex no longer resulted in retractility), have a normal scrotal testis. As a result routine outpatient follow-up of boys with 'retractile testicles', was not thought necessary. It is now clear that there is a small group in whom the retractile testis does not descend as expected; in fact, with growth the testis appears to become more difficult to manipulate into the scrotum, if not actually to ascend (the ascending testis). The probable explanation is that there is a coexisting hernial sac or processus vaginalis which prevents cord lengthening as the boy grows. The implications are that any boy in whom there is the least difficulty in manipulating the testis below the mid-scrotal level should be followed up at least annually.

Incidence

In a study in the late 1950s of more than 3000 babies delivered in a hospital in west London, and followed up for 1 year, Scorer[1] found the incidence of cryptorchidism to be about 0·8 per cent. More recently, a study of orchidopexy rates derived from the Hospital Inpatient Enquiry, suggests that the incidence of cryptorchidism may have doubled in the past 20 years[2]. This latter inquiry was initiated because cryptorchidism is the major risk factor for later testicular malignancy; some 10 per cent of patients with testicular cancer give a history of cryptorchidism.

To confirm the impression of an increase in cryptorchidism an investigation was conducted of all boys born in the John Radcliffe Hospital, Oxford, between November 1984 and October 1986[3]. The overall incidence of cryptorchidism at birth was 5·9 per cent and by 3 months this had dropped to 1·6 per cent. For babies of birthweight $\geqslant 2{\cdot}5$ kg the rate was 4·8 per cent which dropped to 1·4 per cent by 3 months. There was a higher incidence of cryptorchidism in smaller babies and a higher rate of descent by 3 months, i.e. there was a clear decrease in cryptorchidism rate with increasing birthweight. Therefore the suspected increase in cryptorchidism was confirmed. This increase, however, does not match the increase in orchidopexy rates. While there may be some distortion in the orchidopexy figures due, for example, to the inclusion of boys having testicular fixation following torsion, or having orchidopexy associated with herniotomy, the suspicion is strong that orchidopexy is being performed too frequently[4].

The timing of orchidopexy

Review of the literature regarding fertility is complicated by the variability of the reported studies. For example, there is a possibility that those being examined may have had normal retractile rather than abnormal testes, or that the groups examined represent a selected sample, or that methods of semen collection and analysis were different. After analysis of the literature relating to children who underwent orchidopexy between the ages of 4 and 14, Chilvers *et al.*[5] suggested that there was little evidence that operating early or, indeed, operating at all had an effect on subsequent fertility. Of unilateral treated cases 15 per cent were azoospermic and 30 per cent oligospermic, while in bilateral treated cases 42 per cent were azoospermic and 31 per cent oligospermic. It is to be hoped that very early operation will improve these figures, a hope which is encouraged by histological studies of cryptorchid testes which demonstrate that significant morphological changes do not appear until the end of the second year of life.

There is no proof that orchidopexy protects from later malignant change, although it is clearly advantageous for the testis to be in a scrotal position where an abnormality may be recognized early. An intra-abdominal testis appears to be at greater risk of malignant change than an abnormal inguinal testis. It is probable that the factor (or factors) which causes abnormal testicular position is also responsible for the predisposition to malignancy, although the subject is further complicated by the fact that in some adults with testicular cancer the cryptorchidism has occurred in the contralateral testis.

As the tendency for further descent of the testis may continue during the first year of life, especially in low birthweight infants, it is important to avoid too early operation if there is any uncertainty regarding the abnormality of testicular position. If there is no doubt, operation within the first 6 months seems most appropriate on present evidence. Ideally, surgery should not be delayed beyond the age of 2 years. It must be recognized, however, that the operation is technically more difficult in the very young and trauma to the testicular vasculature or vas is a real risk. Some estimates in the past, when operation was usually performed in older children, have put the postorchidopexy atrophy rate as high as 10 per cent. This is not a procedure to be undertaken by the unsupervised surgical trainee.

It has been accepted that in terms of psychological disturbance the most unsuitable ages for hospitalization and operation are between 18 months and 4 years. It may well be that day case admission with a parent continually present in the ward, and accompanying the child to the anaesthetic room has made this less important. However, with accurate, early diagnosis the surgical treatment of cryptorchidism should in future, for reasons of preserving testicular maturation, be complete by 1 year or 18 months of age. Some boys will undoubtedly escape this diagnostic net in these early years but, it is hoped, will be diagnosed at a pre-school medical examination at 4 years old. Early treatment seems likely to forestall the psychological problems which have been attributed to testicular abnormality; there is now no place for 'waiting to see what happens at puberty'. The insecure or embarrassed adolescent with an absent testis may be offered the cosmetic advantage of a prosthesis.

An abnormal, but palpable testis can almost always be sufficiently mobilized at operation to be placed in the scrotum. Fixation is best performed by placing the testis in a pouch between the dartos muscle and the skin, although some still prefer to place the testis in the opposite scrotal compartment. Fixation to the fascia of the thigh or by the use of rubber bands are of historical interest only.

Adequate mobilization of the testis sited just within the internal inguinal ring or in the inguinal canal itself, sometimes may be difficult, even using additional retroperitoneal dissection[6]. In these circumstances orchidopexy may be staged, initially fixing the cord and testis in the inguinal canal within fine Silastic® sheeting (Dow Corning, Reading, UK). This prevents adhesions, which otherwise make the second stage operation a year or so later both difficult and risky to the testicular vessels. Although this procedure has been criticized on the grounds that the need for it represents inadequate mobilization, it is far preferable to over-zealous mobilization which produces vascular damage.

The true intra-abdominal testis which, at operation, may be diagnosed by preliminary laparoscopy, can rarely be mobilized sufficiently by standard techniques and if there is a normal contralateral testis the most appropriate treatment may be orchidectomy. However, the vasal vessels from the inferior epigastric vessels may be able to maintain the testicular blood supply through collaterals. If this appears to be the case, trial clamping of the short testicular vessels, followed a few minutes later by a small incision into the tunica albuginea to ensure there is fresh bleeding, may allow the testicular vessels to be divided, so providing considerable additional length. It is a matter of judgement whether this manoeuvre should be the first stage of a two stage procedure, or should be followed immediately by placing the testis in the scrotum, for this significant alteration in the position of the collateral vessels may compromise their effectiveness and perhaps account for some of the poor reported results. Microvascular anastomosis of the divided testicular vessels to the inferior epigastric vessels has been practised recently, with a number of small series showing success rates of 60–100 per cent. This method demands considerable microvascular experience and the results of such operations on the very young—before irreversible changes have occurred in the testis—remain to be assessed.

The whole subject of the abnormal testis in childhood has been admirably reviewed by Hazebroek in his book *The Treatment of Cryptorchidism*, published in 1986[7]. Its findings support Russell's views on the importance of operative technique[8] and point to the need for the management of this condition to be a responsibility of paediatric surgeons or general or urological surgeons with specialist experience in children's surgery.

M. H. Gough

John Radcliffe Hospital
Oxford
UK

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Current management of venous thromboembolic disease

Despite improvements in early diagnosis, medical management, and prophylaxis of venous thrombosis, pulmonary embolism continues to be a vexing and frequently fatal problem. Estimates of the incidence of fatal pulmonary embolism in the USA continue to range from 50 000 to 100 000 or more annually[1,2]. In spite of this high incidence, the management of patients with established thromboembolic disease remains controversial.

The initial question faced by the clinician managing a patient with a new diagnosis of deep venous thrombosis is whether to treat with conventional anticoagulation or to attempt to remove the thrombus with one of the newer thrombolytic agents or use a surgical approach. While surgical thrombectomy was commonly performed in the past, it has been abandoned for most deep venous thromboses because of the high rate of rethrombosis. Recently there has been a resurgence in interest in surgical thrombectomy for severe iliofemoral venous thrombosis causing phlegmasia cerulea dolens or phlegmasia alba dolens. The incidence of rethrombosis has been reduced in these patients by the creation of a temporary distal arteriovenous fistula. Nevertheless, the use of surgical thrombectomy should be reserved for this very select group[3]. There have been several studies comparing anticoagulant therapy and thrombolytic drugs for the treatment of acute deep venous thrombosis. Serial venographic studies have shown that heparin is quite effective in preventing extension of the thrombotic process but that only a small amount of thrombolysis occurs during treatment with heparin. In contrast, approximately 50 per cent of patients treated with thrombolytic therapy will have significant lysis of thrombus. It appears that the age of the thrombus is the most important factor in determining the likelihood of lysis[4]. There is a significant cost to this increased lysis, however, and that is the 2·9 times greater incidence of bleeding complications in patients treated with lytic therapy compared with those treated with heparin.

The advocates of lytic therapy for deep venous thrombosis propose that such therapy will result in better preservation of venous valvular function and thus reduce the incidence of late post-phlebitic syndrome and chronic venous insufficiency. As yet, however, there has been no large scale comparative study to support this contention.

Based on current available data, it is recommended that surgical therapy be reserved for patients at immediate risk for venous gangrene due to the phlegmasia syndromes. Fibrinolytic therapy may be considered for patients with extensive venous thrombosis but who do not require immediate surgical decompression and for those in whom lysis of thrombus can occur over 24–48 h. Patients with lesser degrees of venous thrombosis are best treated with conventional heparin anticoagulation and heparin should also be administered to patients following a course of fibrinolytic therapy.

After an episode of venous thrombosis, patients remain at risk of recurrent thrombosis for an undetermined period. Conventionally, patients have been anticoagulated with warfarin following 7–10 days of heparin therapy. The warfarin has been continued for from 3 to 6 months. There is a significant risk of bleeding complications with warfarin and, because of this, recent trends have been to lower the dose to prolong the prothrombin time by a ratio of 1·2 : 1·5 rather than the previous goal of prolongation by a factor of two. The lower dose appears to be equally effective in preventing recurrence of venous thromboembolism and is clearly associated with a lower incidence of bleeding complications[5].

The management of established pulmonary embolism is perhaps even more controversial than the management of simple deep venous thrombosis. Heparin has been compared with no treatment for established pulmonary embolism, but this trial had to be discontinued because of the clear superiority of anticoagulation compared with no treatment[6]. The mortality rate for undiagnosed and therefore untreated pulmonary embolism is over 30 per cent, while the mortality rate for acute pulmonary embolism in patients treated with heparin is less than half this figure. Heparin therapy allows the body's actual fibrinolytic system to lyse sufficient volumes of thrombus to restore right ventricular and pulmonary pressures to normal, but this process requires several weeks[7].

The primary decision facing the clinician caring for a patient with pulmonary embolism is to decide between heparin and one of three thrombolytic agents. Of the five trials comparing fibrinolytic agents with standard heparin therapy, all have shown improved clot lysis in patients treated with fibrinolytic agents compared with patients treated with heparin. However, this has not been translated into improved mortality or

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improved pulmonary function either early or late[8]. In addition, this fibrinolytic therapy has been used at the cost of an increased incidence of bleeding which may be severe or even fatal. It was hoped that with the introduction of recombinant tissue-type plasminogen activator a more thrombus specific lytic agent would be available and that the incidence of bleeding complications would be reduced. However, recent clinical trials using recombinant tissue-type plasminogen activator have also shown a significant incidence of bleeding complications[9]. Additionally, it must be realized that all of the fibrinolytic agents require 7–12 h for maximal lysis and improvement in pulmonary haemodynamics.

It is expected that the use of fibrinolytic agents for pulmonary embolism will increase. Because of the increased incidence of bleeding, however, the use of these agents should be reserved for patients with haemodynamic compromise but who do not require immediate surgical pulmonary embolectomy for survival.

Ligation and permanent interruption of the vena cava in an effort to prevent subsequent embolization of lower extremity or lower vena caval thrombi have been previously recommended. However, the high incidence of severe venous stasis and post-phlebitic syndrome subsequent to complete interruption of the vena cava suggests that this should be done only in extreme circumstances. In 1972, Greenfield introduced an intravascular cone-shaped filter for the purpose of trapping larger emboli. This device has become the most popular intravascular device for prevention of pulmonary emboli and thousands have been inserted. However, these devices are not innocuous. Filters have been found later in the heart[10], in the renal and suprarenal position, as well as in the iliac veins[11]. Perforation and injury to retroperitoneal organs may occur[12]. Current design allows percutaneous insertion through the femoral vein. However, the large size of the catheter and thus the degree of injury to the femoral vein is such that exacerbation of the lower extremity venous thrombosis syndrome by femoral vein thrombosis at the site of cannulation may occur in as many as 40 per cent of insertions[13]. A smaller apparatus for introduction currently being developed may improve this alarming rate, but this new device is not yet available for general use.

The indications for insertion of a filter include pulmonary embolism in the presence of an absolute contraindication to anticoagulation such as recent intracranial haemorrhage or an extensive surgical procedure. It may also be used in patients who experience major bleeding episodes while on anticoagulation for embolism. Recurrent embolism while on adequate anticoagulation therapy is exceedingly rare but is an indication when it occurs. A large number of filters are being inserted for prophylactic reasons[14], but in view of the problems mentioned above, this practice may be viewed with circumspection and requires continued reassessment.

Duke University Medical Center
Durham
North Carolina 27710
USA

R. L. McCann
D. C. Sabiston

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Review

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Metabolic response to sepsis and trauma

R. G. Douglas and
J. H. F. Shaw

Department of Surgery, Auckland Hospital, Park Road, Auckland, New Zealand

Correspondence to:
Associate Professor J. H. F. Shaw

This review examines current knowledge regarding the metabolic responses to trauma and sepsis. The factors which may mediate the responses are discussed and the potential value of pharmacological or nutritional manipulation is reviewed.

Keywords: Metabolic response, sepsis, trauma

The accelerated breakdown of skeletal muscle following significant injury was first identified by Cuthbertson more than 50 years ago[1]. He divided the response into a short-lived 'ebb' phase, corresponding to the period of hypovolaemia and sympathetic activity immediately after injury, and a more prolonged 'flow' phase which is characterized by a negative nitrogen balance. A catabolic state similar to the flow phase of trauma also occurs in patients with established sepsis, and many parallels can be drawn between the metabolic profile of the severely injured and septic patient. This article is a review of the present knowledge of the metabolic responses to trauma and sepsis. Contention persists over some aspects of the nature of these responses and the factors which mediate them, and data and interpretations of the polemical issues will be presented.

The consequences of a prolonged catabolic response are now seen more frequently as intensive care facilities prolong the survival of multiply injured and severely septic patients. Although modern techniques of enteral and parenteral nutrition are able to reduce the rate of consumption of protein and energy reserves it is not yet possible to achieve a positive nitrogen balance in severely stressed patients[2]. The last section of this review discusses the impact of intravenous nutrition on the metabolism of septic and trauma patients and summarizes the results of experimental work with agents which promote protein conservation in this setting.

Mediators of the metabolic response to sepsis and trauma

It is well established that the neuroendocrine response to sepsis and trauma effects many of the observed changes in metabolism (*Figure 1*). More recent work has suggested that inflammatory mediators released from the wound itself or from a septic focus may also play a part in these changes[3]. Despite extensive investigation there remains much conjecture about the nature of the link between tissue insult and the resultant metabolic response.

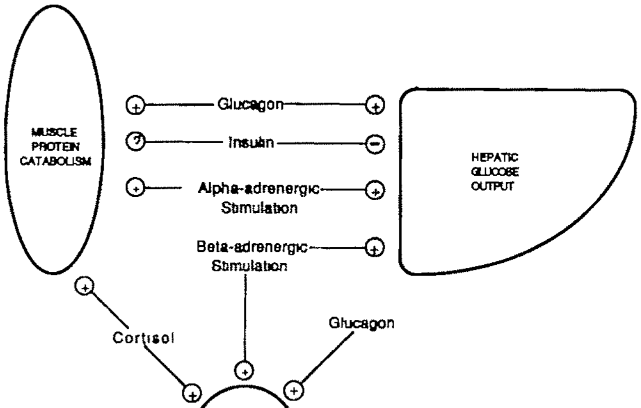
MUSCLE PROTEIN CATABOLISM
Glucagon
Insulin
Alpha-adrenergic Stimulation
Beta-adrenergic Stimulation
HEPATIC GLUCOSE OUTPUT
Cortisol
Glucagon
FFA & GLYCEROL AVAILABILITY

Figure 1 *An overview of the important hormonal regulatory factors in the regulation of metabolism in septic and injured patients FFA, free fatty acid*

The neuroendocrine response

Injury is followed by an outpouring of sympathetic activity and a clearly positive relationship has been established between the injury severity score[4] (ISS) and the plasma concentration of adrenaline, noradrenaline and dopamine[5,6]. The plasma catecholamine levels are maximal shortly after injury, but this response is short lived and the plasma levels have usually returned to the normal range within 24 h[7]. Although it is possible to relate plasma hormonal levels to the ISS score we have recently demonstrated that there is no correlation between the ISS score and the degree of metabolic abnormality seen in patients after blunt trauma[8]. The metabolic response in these patients appears to be an 'all or none' response—the patient with an ISS of 15 is metabolically similar to the patient with a score of 50.

At the same time as the sympathetic nervous system response, the hypothalamic–pituitary axis is also activated. However, the relationship between injury severity and plasma cortisol is not direct: cortisol levels peak at an ISS of 12 and then become lower with more severe injury[9]. In addition, the cortisol response is transient and the plasma cortisol level falls to normal within a few days of injury Furthermore, the correlation between hormonal changes and metabolic abnormalities is difficult to show; for example we have found no correlation between the plasma cortisol level and the degree of alteration in either glucose or protein kinetics[8].

The plasma concentration of growth hormone is raised for 24 h after injury[10], as is that of prolactin. Following thermal injury antidiuretic hormone levels have been reported to be ten times control values[11]. Aldosterone is increased[12], the renin–angiotensin system is activated[13] and glucagon levels rise markedly about 12 h after major injury[14].

Thus, the ebb phase of injury is associated with increased sympathetic activity and an outpouring of counter-regulatory hormones. However, during the stage of maximal nitrogen loss in the flow phase (about 7–10 days after injury) the catecholamine, glucagon and cortisol plasma levels are not raised[13]. This is, however, the time when the plasma insulin level rises to a peak[15].

Although the catabolic response during the postinjury flow phase and established sepsis is similar, there exist differences in the hormonal milieu between these two conditions; the counter-regulatory hormones remain high in septic patients and the elevation of insulin levels is not a consistent feature[13].

There has been a recent attempt to simulate the hormonal responses associated with injury in normal volunteers to elucidate the role of hormones as mediators of the metabolic change seen following trauma[16]. Nine volunteers received a continuous 74-h infusion of the three 'stress' hormones

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(cortisol, glucagon and adrenaline) at a rate which produced plasma levels similar to those seen following mild to moderate injury. The infusion resulted in a significantly raised basal metabolic rate, hyperglycaemia, hyperinsulinaemia and insulin resistance, and a negative nitrogen balance. Further studies with single hormone infusion indicate that there is a synergistic action between the three hormones. The researchers concluded that the simultaneous release of stress hormones may be responsible for mediating the metabolic response to injury.

Inflammatory mediators

It is not possible to explain the complete spectrum of metabolic changes seen in septic and injured patients by the neuroendocrine response as it is presently understood. This has provoked the search for other mediators. Recent research has suggested that interleukin 1, a protein released by macrophages at sites of inflammation, plays a part in the afferent link between damaged tissue and the central nervous system. This new work is discussed further in relation to protein metabolism (see below). Wilmore has recently described synergism in the action of inflammatory and endocrine mediators and concluded that both are integral factors of the metabolic response to sepsis and trauma[3].

Energy production

Cuthbertson's appealingly simple description of a hypometabolic ebb phase and hypermetabolic flow phase[17] has undergone substantial modification in the light of more contemporary research. There is little evidence from clinical studies to suggest that heat production is reduced during the ebb phase[18], and it is likely that the increase in metabolic rate during the flow phase is not as large as previously thought[13]. None the less a modest increase in resting energy expenditure in the flow phase is commonly observed and, in the extreme case of extensive burn injury, this increase may be as great as 100 per cent[19]. The maximal increase in resting energy expenditure coincides with the maximal rate of protein catabolism and occurs around 1 week after injury

Numerous factors have been proposed to account for the extra heat production, such as the increased oxygen consumption of the injured tissues, increased energy expenditure by the heart, the Q_{10} effect of raised body temperature, the thermic effect of accelerated protein breakdown and the heat of evaporation lost from burn surfaces[13,20]. The matter has been the subject of a concise review by Little who concludes that the underlying mechanism is probably a resetting of hypothalamic regulatory control[21] Yet a further explanation has recently been advanced: it is known that in trauma patients there is an increased rate of substrate recycling in which triglyceride is hydrolysed and then re-esterified, and glucose and its glycolytic intermediates are recycled. As there is no net production of free fatty acid or glucose during these cycles but ATP is hydrolysed, such recycling represents an energy drain Wolfe *et al.* have recently quantified the energy dissipated by such substrate recycling and, although their methodology grossly underestimates the extent of these processes, they conclude that it is possible that these cycles provide the principal biochemical explanation for the increased heat production seen in trauma patients[22].

Glucose metabolism

The post-traumatic ebb phase and the earliest stage of sepsis are both characterized by hyperglycaemia[23]. This rapidly established response is initially the result of enhanced glycogenolysis[24] and later a consequence of increased glucose production coupled with reduced peripheral utilization[23]. Sympathetic activity and circulating adrenaline provide the stimulus for hepatic glycogenolysis and encourage glucagon release while simultaneously inhibiting insulin release from the endocrine pancreas[25–27] The release of cortisol probably plays a facilitatory part in this response[28] The plasma glucose levels subsequently fall during the post-traumic flow phase to less elevated or normal levels[29,30].

However, the plasma glucose level gives little indication of glucose turnover and this has been the subject of much recent investigation. It is generally agreed that in septic and flow phase trauma patients, glucose turnover is increased and that gluconeogenesis is enhanced despite freely available plasma glucose, but there is controversy over changes in glucose oxidation in these situations[31].

Gluconeogenesis

In health, gluconeogenesis is effectively inhibited by an increase in blood glucose levels. However, hepatic glucose production is maintained at normal or elevated rates during the high flow response to trauma or sepsis[32–34] despite the hyperglycaemia characteristic of such severely ill patients The suppression of gluconeogenesis by glucose infusion is very much less effective in septic and trauma patients than in normal volunteers[35–37]. This reduction in the suppressibility of gluconeogenesis is probably caused by the increased availability of gluconeogenic substrates occurring in a favourable hormonal milieu[23,26,28]. In severely stressed patients, muscle glycogenolysis and the metabolism of hypoxic tissues produce lactate, glycerol is released from adipose tissue, and plasma alanine levels are increased as a result of enhanced proteolysis[34,38]. In burn patients it has been determined that lactate is quantitatively the most important gluconeogenic substrate[23]. Previously we have demonstrated an increase of 40 per cent in the rate of appearance of alanine and a 100 per cent increase in the rate of appearance of glycerol and availability of lactate in trauma patients[8]. On the basis of 2 mol of either alanine, glycerol or lactate being required to produce 1 mol of glucose it is likely that this substantial increase in three carbon substrates would be adequate to explain the observed increase in basal glucose appearance seen in these patients.

However, in recent work by Jahoor *et al.*[39] in burn patients in which both insulin and glucagon concentrations were lowered simultaneously by infused somatostatin, hepatic glucose production decreased despite an increase in the delivery of alanine to the liver. These results suggest that glucose production is controlled at the liver and not by precursor supply.

Glucose oxidation

Although most investigators report that glucose oxidation is increased during the high flow phase and sepsis in absolute terms, there remains disagreement over whether glucose is oxidized as efficiently as in healthy volunteers[40]. The Manchester Trauma Unit researchers have found an increase in glucose oxidation in relation to plasma glucose in injured patients, which they interpreted as a consistent response of substrate mobilization and oxidation[30]. However, the situation is far from clear: there exists a considerable body of data derived from isotopically labelled substrate studies which suggests that glucose is oxidized less efficiently in septic and trauma patients[8,29,31,41–43]. The recently reported reduced activity of the pyruvate dehydrogenase complex in septic rats suggests that intracellular derangements in enzymatically controlled pathways may account for the observed reduced efficiency of glucose metabolism[44].

It is germane to the interpretation of the data reported on glucose kinetics that the rate of glucose clearance from the plasma is not related to the rate of glucose oxidation or even to the percentage of glucose uptake oxidized[45]. Therefore, it is unlikely that reduced glucose oxidation is simply a consequence of the prevailing insulin resistance.

Insulin

Although changes in insulin release and responsiveness in septic and trauma patients have been well documented[46–48], the role of this hormone in the metabolic changes associated with these conditions remains to be clearly defined.

The sympathetic discharge following severe burns has been associated with an inhibition of insulin release[25], although a low plasma insulin level is not a consistent feature of the immediate postinjury period[15]. Plasma insulin levels subsequently rise to reach a peak several days after injury of up to three times basal levels[49]. This coincides with the period of maximal catabolism[50].

During the flow phase, the plasma insulin level is inappropriately high for the plasma glucose concentration[30] with the pancreas showing a normal or augmented response to glucose infusion[51,52]. However, this phase of the metabolic response is characterized by insulin resistance.

The high levels of insulin fail to suppress glucose production, and there is a reduction in glycogen storage[29], lipolysis and fat oxidation[53] Frayn has demonstrated a highly significant correlation ($r=0{\cdot}97$) between the plasma insulin concentration and nitrogen loss in trauma patients and concludes from this finding that protein turnover is resistant to the normal anabolic effect of insulin[15]. However, Jahoor *et al.* have found in burn patients that insulin acts to conserve protein by restraining the release of amino acids from peripheral tissues[39]. Wilmore has similarly demonstrated a protein anabolic effect of insulin despite profound insulin resistance to carbohydrate in the skeletal muscle of injured patients[54]. The nature of the changes in insulin receptors has not been accurately characterized, although it is likely that there are changes at both the receptor and post-receptor level[55]. Experimental animal models most clearly implicate glucocorticoids as a cause of insulin resistance[56], although the mechanism of this response is yet to be fully elucidated.

The adaptive value of fuel store mobilization

The mobilization of fuel reserves in trauma and sepsis is common to several species of laboratory animal studied and is likely to be of adaptive value. Infusion of hypertonic glucose has been shown to decrease mortality in pigs following severe haemorrhage[57] and this manoeuvre has also resulted in a rapid increase in blood pressure in recently injured battle casualties[58]. It has been suggested that the observed pressor effect is due to a mass action effect of glucose increasing myocardial glucose uptake and hence the availability of glucose for anaerobic glycolysis[58]. Hyperglycaemia will also compensate for intravascular fluid losses.

The increase in gluconeogenesis and its reduced supressibility during exogenous glucose administration in the post-trauma flow stage and in sepsis may reflect the influence of the damaged and reparative tissues on the rest of the body[59]. The cells involved in inflammation and wound repair rely on glucose as a primary fuel which they predominately metabolize anaerobically. The wound may be looked upon as a privileged organ whose glucose demands can account for most of the approximate doubling in glucose turnover seen in severely burned patients. Wilmore concludes that the increased glucose turnover provides essential fuel for inflammatory and reparative tissue which optimizes host defences and ensures wound repair[54].

Fat metabolism

The complex changes in the mobilization and oxidation of fat in sepsis and trauma have not been as fully unravelled as those in carbohydrate metabolism. Again it is appropriate to discuss the post-trauma changes in the ebb and flow phase, and again there are parallels to be drawn between the flow phase and established sepsis.

Lipolysis is enhanced immediately after injury by the stimulation of the sympathetic innervation of adipose tissues and by raised plasma adrenaline, glucagon and cortisol levels[38]. Growth hormone may also play a part in this response[60]. The accelerated lipolysis occurs despite the prevailing hyperglycaemia and raised plasma insulin[61]. There is, however, little correlation between plasma free fatty acid levels and the severity of the trauma[24,62] This is probably a result of the reduced perfusion of adipose tissues which often follows severe trauma, so that the supply of albumin carriers for released free fatty acids is inadequate[63]. In addition, the plasma free fatty acid level is lowered further by the lactic acidosis of systemic hypoxia which encourages re-esterification[64].

Septic patients have a lower respiratory quotient (RQ) than non-septic controls, and worsening sepsis is frequently accompanied by progressive falls in RQ. These findings have been corroborated by isotopic studies and suggest that increased fat oxidation may be an important feature of the altered metabolism seen in sepsis[65–67]. During the first few days after severe injury the RQ rises from a value of close to 0·7 to one that indicates that carbohydrate is the major fuel[13]. Glucose infusion in normal volunteers inhibits fat oxidation and the RQ rises above 1·0 as the excess glucose is deposited as triglyceride. However, in patients with severe sepsis, although the RQ rises following glucose infusion it does not reach a value of 1·0 indicating that fat continues to be the main substrate for oxidation[51].

Under most circumstances the rate of uptake of free fatty acids is directly proportional to their plasma concentration[68]. However, the increase in fatty acid oxidation in sepsis and trauma is not 'substrate led' as the plasma levels of free fatty acid are often quite low[30]. This suggests that there are changes in the intracellular metabolism of fat in these patients[38].

The preference for fat as an energy substrate is more pronounced in septic than in trauma patients[66]. Using the sepsis severity scale developed by Elebute and Stoner[69], it has been shown that there exists a positive relationship between fat oxidation and sepsis severity, whereas there is a negative relationship with glucose oxidation[66].

Less is known about changes in triglyceride metabolism. It has been reported that the concentration of triglyceride in plasma is elevated in Gram-negative sepsis[70] and after injury[15]. There is presently no isotopically-labelled triglyceride suitable for infusion into patients, but studies in septic animals have revealed that the increase in triglyceride concentration is owing to an accelerated rate of production of triglyceride, and in particular very low density lipoprotein, rather than the response being secondary to a decrease in triglyceride clearance[71,72]. The increase in activity of adipose tissue lipoprotein lipase is consistent with the postulated increase in very low density lipoprotein turnover[73].

Ketone metabolism

Simple starvation is attended by ketosis As ketone bodies can serve as alternative energy substrates for many tissues, they reduce whole body glucose demand and therefore gluconeogenesis from protein. However, in severe sepsis and, to a lesser extent, trauma there is a blunting of the adaptive ketonaemic response and its subsequent nitrogen conservation[74,75]. It is likely that the increased insulin levels seen in stressed surgical patients are responsible for the impaired production of ketone bodies[76], although reduced activity of hepatic acylcarnitine transferase has also been implicated[77].

Protein metabolism

The negative nitrogen balance described by Cuthbertson[1] has been similarly demonstrated in septic patients[78]. When this response is prolonged, the resultant protein depletion plays a major part in the pathogenesis of multiple organ failure which develops in severely injured or septic patients[79] A detailed understanding of the nature and mechanism of the protein loss is important to provide a basis for giving more effective nutritional support and offers the alluring possibility of metabolic manipulation in such cases.

Whole body kinetics in sepsis and trauma

A net protein loss may result from a relative decrease in whole body protein synthesis, an increase in catabolism, or a combination of both mechanisms. The varied responses reported following elective surgical procedures, musculoskeletal trauma, burns and sepsis are summarized in *Table 1*. The trauma

Table 1 *Protein synthesis and catabolism rates in sepsis and after surgery and trauma*

Reference	Subjects	Methodology	Synthesis	Catabolism	Comment
Crane *et al.* 1977[82]	Elective orthopaedic $n=11$	Oral [^{15}N]glycine	↓	No change	
O'Keefe *et al* 1974[80]	Elective abdominal operations $n=4$	Infused [^{14}C]leucine	↓	No change	Reduced postoperative calorie intake 2 cancer patients
Kien *et al.* 1978[81]	Skin reconstruction in children $n=6$	Infused [^{15}N]glycine	↓	No change	Postoperative intake maintained
Rennie and Harrison 1984[88]	Abdominal surgery $n=11$	Skeletal muscle efflux of 3-methylhistidine and tyrosine	↓↓	↓	Postoperation all on IVN 10 cancer patients
Kien *et al* 1978[83]	Burns, children $n=11$	Infused [^{15}N]glycine	↑	↑↑	Controlled nutritional support
Birkhan *et al.* 1980[84]	Multiple trauma $n=6$	Infused [^{14}C]leucine	↑	↑↑	
Shaw and Wolfe[8]	Trauma $n=43$	Infused [^{15}N]lysine and [^{14}C]urea	↑	↑↑	Some on IVN
Shaw *et al* 1986[117]	Sepsis $n=22$	Infused [^{15}N]lysine and [^{14}C]urea	↑	↑↑	Net protein catabolism continued despite IVN

IVN, intravenous nutrition

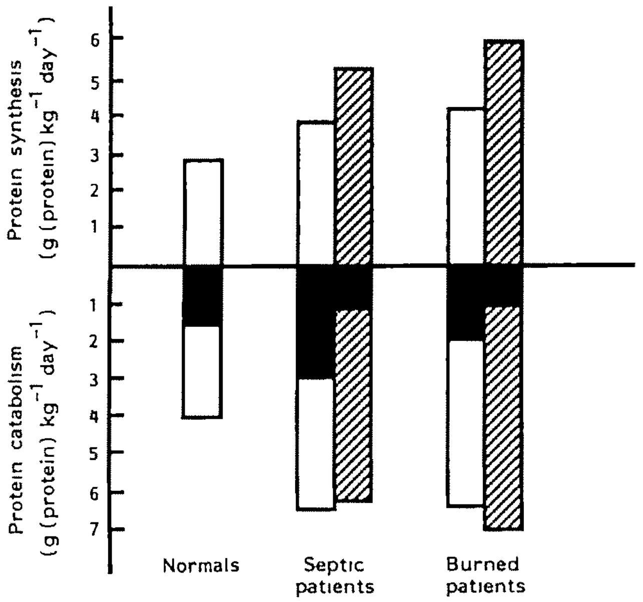

Figure 2 *Rates of total protein synthesis, total protein catabolism and net protein catabolism in normal volunteers, septic patients and in burned patients. In septic and burned patients the rate of net protein catabolism is significantly greater* ($P<0.05$) *than in volunteers. Providing intravenous nutrition reduces net protein catabolism by significantly increasing total protein synthesis. The rate of total protein catabolism remains unchanged (modified from Shaw and Wolfe, 1987*[31]*.* □*, Basal nutrition (post-prandial at 12 h in normal volunteers),* ▨*, intravenous nutrition,* ■*, net protein catabolism*

of elective surgery results in an inhibition of protein synthesis, whereas catabolism proceeds at an unchanged rate[80-82]. However, in severe trauma involving multiple fractures or burns, or in septic patients, both synthesis and catabolism are increased, with the rate of protein degradation outstripping that of production[8,42,83,84] (*Figure 2*). The cause of this disparity in response is not clear, but it is likely that the postoperative changes primarily reflect the effect of starvation rather than the response to trauma *per se*. It is noteworthy that the acute metabolic response to severe injury and sepsis is the direct reverse of that seen in starvation in which both protein synthesis and degradation are reduced[85,86].

The preceding description of the relative changes in the relationship between net protein synthesis and catabolism oversimplifies the situation as it exists in the clinical setting as it does not include the influence of protein intake. This deficiency is rectified in the model developed by Clague and his colleagues[87], in which they propose that the protein breakdown in response to trauma is largely obligatory, whereas synthesis increases with substrate availability. Accordingly, provision of adequate protein can reduce net nitrogen loss after trauma.

Changes in skeletal muscle

Skeletal muscle is the major site of nitrogen storage and of nitrogen loss, although the contribution of other tissues such as skin, gut and lungs may not be insubstantial[88]. The rate of release of 3-methylhistidine, an amino acid derived exclusively from actin and myosin and excreted unchanged, has been used as an index of the rate of skeletal muscle breakdown[89]. Considerable increases in the rate of production of 3-methylhistidine have been seen in severely traumatized and septic patients[90], whereas no increase occurs following orthopaedic operations and minor injuries[91]. Although recent doubts have been voiced about the specificity of 3-methylhistidine as an indicator of skeletal muscle breakdown[92], other investigators have provided sound arguments for its continued use[93].

In injury, the increased rate of protein release from skeletal muscle does not simply represent the degradation of damaged tissue; there is increased loss of 3-methylhistidine and changes in skeletal metabolism in muscle undamaged by trauma[94,95].

The technique of percutaneous needle biopsy of human muscle[96] has enabled investigation of the intracellular metabolic derangements. The changes in intracellular amino acid concentration following elective surgery, trauma and in sepsis are similar, suggesting a common response to varying types of insult[97-99]. The response consists of an increase in essential amino acids, particularly branched chain amino acids, and reduction in non-essential amino acids largely as a result of a 50 per cent decrease in the level of intracellular glutamine[97] The cause of these changes remains a matter for conjecture[95-100].

Hepatic protein metabolism

The data of studies of whole body protein metabolism represent the summation of response of the body tissues, but fail to reflect variation in kinetics between different tissues In both severe trauma and sepsis, whereas skeletal muscle catabolism exceeds synthesis there is a net increase in the production of hepatic structural and secretory proteins[101,102].

The teleological explanation of the autocannibalism of muscle tissue in response to stress is that this mechanism allows greater than normal quantities of amino acids to be available to the liver for gluconeogenesis, oxidation and the synthesis of proteins involved in immune defence and wound healing[26,34,103]. This increased hepatic synthesis occurs at a time of depressed efficiency of other hepatic cellular functions[104,105], reflecting the high priority of this function in sepsis and trauma[106].

Mechanism of protein loss

The catabolism of muscle protein reserves to provide substrate for increased hepatic synthesis to defend against infection and promote wound healing is an appealing explanation of the changes in protein metabolism seen in sepsis and trauma. This presents the challenge of delineating the neuroendocrine changes which mediate this response.

It is known that physical rest, fever, starvation, glucocorticoids and insulin resistance[79,85,102] are associated with an increased net rate of protein breakdown, but that none of these stimuli induces protein catabolism to the degree seen in sepsis and trauma[107]. Glucocorticoids cause an increased amino acid release, increased oxidation of leucine by skeletal muscle and favour hepatic conversion of amino acid to glucose. However, it is generally believed that glucocorticoids have primarily a permissive role and are not responsible for the overall protein catabolism seen in sepsis and trauma[26]. We have demonstrated that glucagon plays a part in accelerating protein breakdown in trauma patients[108].

Recent work has suggested that factors produced by leucocytes may be central in promoting the changes in protein metabolism in sepsis and trauma. Interleukin 1, a polypeptide synthesized by macrophages as part of the inflammatory response, causes fever and leucocytosis[109]. Rat muscle incubated with interleukin 1 showed a stimulated rate of proteolysis but the protein synthesis rate was unaffected[110]. These effects may be mediated by prostaglandin E_2 as the interleukin 1 increased prostaglandin E_2 production and the catabolic effects of interleukin 1 can be abolished by the addition of indomethacin. When injected into the peritoneal space of rats, interleukin 1 increased the rate of synthesis of hepatic secretory and structural proteins[111,112]. The field of inflammatory mediators is advancing rapidly as new proteins are isolated and their actions described.

Consequences of a prolonged catabolic state

The breakdown of skeletal muscle that occurs in septic and trauma patients may be of adaptive advantage as the convalescing animal is provided with adequate energy substrates and amino acids for hepatic protein synthesis. However, if this catabolic response is prolonged the loss of body protein can pose a threat to survival by resulting in pulmonary and cardiovascular insufficiency, and impaired immune function and wound healing[26]. It is for these reasons that attempts have been made to reverse or at least slow down protein catabolism in critically ill surgical patients.

The effects of nutritional support

The optimal nutritional support of severely injured and septic patients has been the subject of intensive investigation. As such patients have a basal metabolic expenditure elevated by 20 per cent or more above normal[31] and as they can lose as much as 40 g nitrogen a day[113], they exhaust their energy and protein reserves much more rapidly than non-stressed patients. Although normal hospital food is the most efficient means of providing calories and protein to these patients, their gastrointestinal system is frequently unable to cope and intravenous nutritional support is indicated.

Septic and injured patients require approximately 40 kcal kg^{-1} per day[114] and this energy requirement has traditionally been supplied as glucose. Glucose infusion has been demonstrated to be a simple and effective means of conserving body protein in severely stressed patients[42]. However, there has been considerable interest in the role of fat as a major and perhaps preferred energy substrate in septic patients and this debate has recently been reviewed by Long[115]. We have used isotopic tracer methodology to demonstrate that lipolysis and fatty acid oxidation are enhanced in sepsis[41,43,67], but whether fat has a greater protein sparing effect than glucose in this setting is yet to be resolved[116].

Despite recent advances in intravenous nutritional support there are several reports indicating that a positive nitrogen balance cannot be achieved in septic or severely traumatized patients[2,88]. Intravenous nutrition (IVN) reduces the net rate of loss of protein by increasing the rate of protein synthesis. However, the capacity to increase synthesis by providing substrate falls short of the increased protein catabolism which proceeds uninfluenced by nutritional support[8,117].

The failure of standard IVN regimens to achieve nitrogen retention in severely stressed patients has led to the investigation of more exotic mixtures. The use of branched chain amino acids to encourage protein anabolism has received much recent attention. Branched chain amino acids play an important part in the regulation of muscle synthesis[118,119], and muscle biopsies of injured and septic patients have shown signficant increases in the intracellular concentration of branched chain amino acids[120]. It has been postulated that this may provide a stimulus for protein synthesis[97]. Series in which postoperative patients have been infused with branched chain amino acids alone[121], with branched-chain-amino-acid-enriched IVN[122] or with α-keto-isocaproate, the ketoacid breakdown product of leucine[123], have shown patients to have improved nitrogen balance, presumably on the basis of increased muscle synthesis. As yet there are no data from prospective trials to support the routine use of such modified IVN mixtures.

Pharmacological manipulation

Hormonal blockade

Several approaches have been taken in attempts to attenuate the catabolic response of severe surgical illness by hormonal blockade. Epidural anaesthesia abolishes the postoperative release of catecholamines and cortisol and has been shown to improve the cumulative nitrogen balance over a 5-day postoperative period in women after hysterectomy[124]. Using isotopic tracer methodology we have recently studied the effects of epidural anaesthesia in 23 patients who had recently undergone extensive surgical procedures[125]. There was a 20 per cent decrease in the rate of production of glucose with a parallel reduction in glucose oxidation, and net protein catabolism as measured by the rate of appearance of [^{14}C]urea was reduced by 11 per cent.

The sympathetic response may also be attenuated with specific pharmacological antagonists. Sympatholytic drugs have been demonstrated to reduce the degree of hypermetabolism in burn patients[126]. In our laboratory we have studied the effects of α and β blockade produced by infusions of phentolamine and propranolol respectively in stressed patients receiving intravenous nutrition[127]. Our data demonstrate that the role of the sympathetic nervous system in the promotion of endogenous glucose turnover in such patients is primarily a β-adrenergic effect, whereas the promotion of protein catabolism is mainly an α-adrenergic effect.

Considerable interest in the role of prostaglandins as effectors of the stress response has been aroused by the recent work on interleukin 1. However, decreasing prostaglandin synthesis with cyclo-oxygenase inhibitors does not reduce muscle catabolism in septic or thermal injury models in animals[128,129] or in septic patients[108], and their use exposes patients to side-effects such as peptic ulceration and impaired haemostasis.

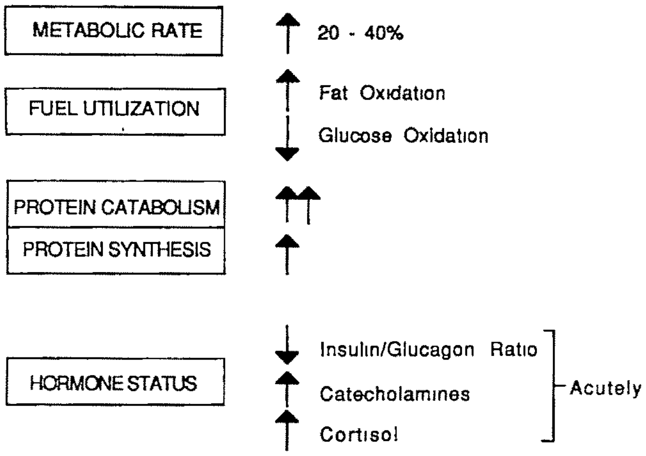

Figure 3 *Summary of the metabolic changes associated with critical surgical illness (modified from Shaw and Wolfe, 1987*[31]*)*

Anabolic hormones

The use of anabolic hormones to attenuate the rate of breakdown of body reserves is an appealing proposition. Insulin has been shown to improve nitrogen balance in trauma patients[130], but was found to have no effect on the gain of body nitrogen or fat when used as an adjuvant with a 2-week course of IVN[131]. Similarly, anabolic steroids have improved the nitrogen balance in postoperative patients[132], but have not been demonstrated to improve the efficacy of IVN[133].

Interest in the therapeutic role of human growth hormone has increased since 1985 when gene recombinant technology enabled its manufacture on a scale which makes its use as a pharmacological agent feasible. Several early investigators reported improved nitrogen balance in burn patients to whom growth hormone was administered[134–36]. More recently Ward and colleagues have demonstrated a favourable influence of growth hormone on protein kinetics in postoperative patients[137] However, the therapeutic role of growth hormone in catabolic patients awaits further definition.

Discussion (*Figure 3*)

The increased release of hormones, particularly adrenaline, glucagon and cortisol, mediate many of the metabolic changes seen in sepsis and trauma. The role of interleukin 1 has yet to be precisely defined, but there is increasing evidence that substances released from damaged tissue are at least partly responsible for the accelerated proteolysis seen in severe surgical illness.

Glucose turnover is increased in sepsis and trauma, but glucose is oxidized with reduced efficiency. There is evidence to suggest that fat is the preferred energy substrate in septic and, to a lesser degree, injured patients.

In critical surgical illness the rates of both protein synthesis and catabolism are increased. However, the increase in catabolism is of greater magnitude resulting in a net breakdown of protein and, if prolonged, muscular wasting, cardiopulmonary insufficiency and immune compromise.

The provision of sufficient energy substrates and nitrogen does not reduce the catabolic response but encourages protein synthesis, decreasing net catabolism. Numerous substrate, hormonal and pharmacological manipulations have been tried to improve the nitrogen balance in surgical patients who are severely ill. To date, the clinical efficacy of none has been conclusively proved.

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Prediction of outcome in patients with acute variceal haemorrhage

S. Jacobs, R. W. S. Chang*, B. Lee*, A. Al Rawaf*, N. C. Pace and I. Salam†

Departments of Anaesthesia,
*†Gastroenterology and *Surgery,*
Riyadh Armed Forces Hospital,
P.O. Box 7897, Riyadh 11159,
Saudi Arabia

Correspondence to: Dr S. Jacobs

Prediction of outcome in 87 patients following acute bleeding oesophageal and gastric varices due to portal hypertension from chronic liver disease was studied at our hospital over a 30-month period. The overall mortality rate was 26 per cent (23/87), with the operative mortality rate (50 per cent) being more than triple the non-operative mortality rate (14 per cent). The initial prothrombin time ratio (PTR) alone was significantly different in survivors and non-survivors both in the operated and non-operated patients. The only survivor in the whole material with a PTR $\geqslant 2{\cdot}2$ *was a patient who was transferred and underwent successful liver transplantation elsewhere. Among operated intensive care unit (ICU) patients, the Glasgow predictor gave a mean probability of discharge of 0·81 (s.d. 0·15) in 13 survivors and of 0·35 (s.d. 0·35) in the 15 non-survivors* ($P < 0{\cdot}001$)*. In the 11 non-operative ICU patients, who had failed sclerotherapy, the Glasgow predictor could not be validated. Fourteen ICU deaths were associated with significant hypotension defined as a systolic blood pressure* <90 *mmHg for* >1 *h.*

Keywords: Outcome prediction, gastric and oesophageal varices, haemorrhage

Massive bleeding from ruptured oesophageal and/or gastric varices is the main complication of portal hypertension from chronic liver disease[1]. Conservative management with the addition of sclerotherapy works well in the majority of patients[2]. A high mortality rate (50 per cent) has been reported in patients who are either unsuitable for sclerotherapy (e.g. those with gastric varices) or who have failed sclerotherapy and who require emergency surgery for the management of their acute variceal haemorrhage[3]. Severe acute bleeding from oesophageal and gastric varices forms an appreciable component of our total intensive care unit (ICU) workload. We have noticed a high mortality rate in our practice, especially in postoperative patients who were considered to require emergency surgery for the control of their bleeding gastric varices. Vast amounts of blood are frequently expended on these patients, often with little impact on outcome. We therefore felt that a reliable predictor of hospital outcome was required to assist us in deciding which patients were likely to survive an operative procedure and justify the expenditure of large volumes of blood.

The work of Garden *et al.*[4] showed that three variables: the initial prothrombin time ratio (PTR), serum creatinine and the presence or absence of encephalopathy were independently predictive and, using them in a derived regression equation, they were able to demonstrate that a probability of discharge figure of 0·66 divided the high risk from the low risk patients. They successfully predicted outcome in 90 per cent of their admissions. We compared the Glasgow predictor with the value of the initial PTR taken as soon as possible after admission to hospital. In our practice it had been our clinical impression that the degree of elevation of the PTR alone gave a good correlation with outcome in patients with acute bleeding gastric and oesophageal varices, both in operated and non-operated cases. We were also interested to ascertain if the presence of intra-operative hypotension for surgical patients and hypotension in the first 24 h of admission for medical patients was an important additional factor in determining outcome.

Patients and methods

All patients known to be suffering from acute bleeding oesophageal and/or gastric varices due to chronic liver disease admitted to the Riyadh Armed Forces Hospital over a 30-month period (March 1985–August 1987) were studied, those who required admission to our six-bedded ICU were studied prospectively, whereas those managed on the general wards were studied retrospectively. These patients constituted the entire hospital admissions of acute variceal haemorrhage during the study period. All patients had fibreoptic endoscopic confirmation of bleeding from oesophageal or gastric varices. Our initial management of these patients was conservative Routine resuscitation was performed with oesophageal tamponade when necessary The few patients requiring oesophageal tamponade in the presence of encephalopathy were routinely intubated with a cuffed endotracheal tube in the ICU

We identified two groups of patients admitted to our ICU

1 Operative patients diagnosed in the ICU or endoscopy room as bleeding from predominantly gastric varices and who were considered to require emergency surgery (variceal ligation, gastric transection and splenectomy) for the control of their haemorrhage. No patient in this series underwent a shunt operation. These patients were routinely admitted to ICU postoperatively.

2 Non-operated patients diagnosed as suffering from predominantly oesophageal varices who were managed in the ICU because of severe bleeding following failed sclerotherapy They were considered too ill to be managed on the general wards.

All ICU patients had the first recorded values of the PTR, serum creatinine and the presence or absence of encephalopathy on admission to hospital noted. Our PTR is an international normalized ratio based on a direct calibration of our thromboplastin reagent against the World Health Organization international reference preparation The upper limit of normal in our population is 1·2 A derived regression equation as suggested by Garden *et al.*[4] was utilized to estimate the probability of discharge from the three variables already mentioned

$$\ln(P/1-P)=10-(4{\cdot}3\times \mathrm{PTR})-(0{\cdot}03\times \mathrm{Creat.})-(0{\cdot}85\times \mathrm{ENC})$$

where P is the probability of discharge; ENC is $+1$ in presence of encephalopathy and -1 in absence of encephalopathy; and Creat. is the the serum creatinine in SI units

Our ICU patients also had their APACHE II score recorded on the day of admission to the unit[5] The APACHE II system is based on deviations from normal of 11 acute physiological variables including the mean systemic arterial blood pressure and the Glasgow Coma Scale. Age, defined chronic ill-health and emergency surgery were also taken into consideration The most deranged value of the 11 physiological variables but best Glasgow Coma Scale were chosen from the first day's data. Patients with a day 1 APACHE II score >35 were predicted to die[6] The APACHE II risk of death was obtained from a multiple logistic regression equation using coefficients devised by Knaus *et al.*[5] for certain specific diagnostic categories

ICU patients' blood pressures were recorded on anaesthetic charts in operative cases and these were assessed immediately after surgery to

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Table 1 *Basic characteristics of 39 intensive care unit patients with acute bleeding oesophageal varices*

	n	%
Male	37	95
Female	2	5
Mean age (years)	50	
Operated patients	28	72
Non-survivors	15	54
Non-operated patients	11	28
Non-survivors	3	27
ICU outcome		
Survivors	31	79
Non-survivors	8	21
Mean ICU stay (days)		
Survivors (s.d.)	4·9 (7·3)	
Non-survivors (s.d.)	6·3 (5·5)	
Hospital outcome		
Survivors	21	54
Non-survivors	18	46

ICU, intensive care unit

ascertain if any significant hypotension, defined as a systolic blood pressure <90 mmHg for >1 h, had occurred. The presence or absence of significant hypotension was also noted in non-operative cases in the first 24 h of admission to the ICU. The total amount of blood given to each patient during their stay in hospital was also recorded. All patients who were operated on were given liberal quantities of fresh frozen plasma routinely during the course of surgery and other clotting factors were also administered as required. We endeavoured to find the cause of the chronic liver disease in all our patients using serological investigations in conjunction with intraoperative and/or percutaneous liver biopsies. All patients who were discharged alive from the ICU were followed up until hospital discharge or death.

The 48 patients treated solely on the general wards during the same 30-month period as the ICU series had the following data collected retrospectively: age, sex, hospital outcome details, initial PTR, endoscopic details and cause of chronic liver disease.

Predictive power of the predictive model using the PTR was calculated as follows:

$$\text{Sensitivity}=\frac{\text{PredDDead}}{(\text{PredDDead}+\text{PredADead})}\times 100$$

$$\text{Specificity}=\frac{\text{PredAAlive}}{(\text{PredAAlive}+\text{PredDAlive})}\times 100$$

$$\text{Predictive value of dying}=\frac{\text{PredDDead}}{\text{Total predicted to die}}\times 100$$

$$\text{Predictive value of living}=\frac{\text{PredAAlive}}{\text{Total predicted to live}}\times 100$$

$$\text{Correct}=\frac{(\text{PredAAlive}+\text{PredDDead})}{\text{Total patients}}\times 100$$

where PredDDead are patients who were predicted to die and died; PredDAlive are patients who were predicted to die and lived; PredAAlive are patients who were predicted to live and lived, and PredADead are patients who were predicted to live and died.

All data were collected on special forms and entered into a microcomputer (IBM AT), using a program written in dBASE III Plus (Ashton–Tate) by one of us. This was utilized to generate APACHE II scores, risks of death, probability of discharge values and for performing statistical calculations. Student's t test was used where appropriate.

Results

Out of a total of 87 adult patients with acute variceal bleeding admitted to our hospital over a 30-month period 23 (26 per cent) died. Thirty-nine patients (45 per cent) were admitted to our ICU and 48 (55 per cent) were managed entirely on the general wards. There were no readmissions to the ICU; readmissions to the ward were not taken into account in our analysis. Among the 39 ICU patients there were 18 (46 per cent) hospital deaths. The basic characteristics of these patients are shown in *Table 1*. There were 28 surgical and 11 non-surgical cases. *Table 2* shows the causes of chronic liver diseases in the ICU patients; 61 per cent of cases were caused by schistosomiasis and hepatitis B. The large preponderance of male to female patients (18·5:1) in this series can be partly explained by the higher incidence of schistosomiasis[7] and hepatitis B virus[8] among Saudi Arabian men.

The mean APACHE II scores, risks of death, the mean APACHE II blood pressure scores, the mean probability of discharge and its component variables, the presence of significant hypotension and the total amount of blood utilized by the ICU survivors and non-survivors are compared in *Table 3* for both operative and non-operative cases. In the operated ICU group the mean APACHE II scores of survivors and non-survivors were 14·6 (s.d. 3·3) and 22·5 (s.d. 9·5) respectively and mean risks of death were 19·6 per cent (s.d. 10·0) and 43·2 per cent (s.d. 26·3) respectively ($P<0{\cdot}01$ for both). Five of the 18 ICU patients who died had a day 1 APACHE II score >35 and were predicted to die.

The probability of discharge among operative ICU patients was 0·81 (s.d. 0·15) in survivors and 0·35 (s.d. 0·35) in non-survivors ($P<0{\cdot}001$). The PTR was the only variable in the Glasgow predictor that was significantly different between survivors, 1·54 (s.d. 0·20) and non-survivors, 2·1 (s.d. 0·41) with $P<0{\cdot}001$. This was reflected in the amounts of blood required by non-survivors (mean 31 units/patient) which was three times that required by survivors (mean 10 units/patient).

In the non-operated ICU group (11 patients) the mean APACHE II score among survivors was 13·8 (s.d. 5·0) and in non-survivors was 22 (s.d. 5·3) with $P<0{\cdot}05$ and mean risk of death was 28·6 per cent (s.d. 13·8) in survivors and 66·2 (s.d. 4·4) in non-survivors ($P<0{\cdot}005$). The mean APACHE II blood pressure score was 0·75 (s.d. 1·0) in survivors and 3·3 (s.d. 1.2) in non-survivors ($P<0{\cdot}01$). The Glasgow probability of discharge values were not significantly different between the survivors and non-survivors. The mean serum creatinine was 104·5 μmol/l (s.d. 56·4) in survivors and 215·5 μmol/l (s.d. 70·9) in non-survivors ($P<0{\cdot}025$). Also the PTR was 1·7 (s.d. 0·3) in survivors and 2·5 (s.d. 0·5) in non-survivors ($P<0{\cdot}01$).

The predictive value of the first PTR and the presence or absence of significant hypotension among operative and non-operative cases is analysed by histograms in *Figures 1* and *2* respectively. *Figure 1* demonstrates that all operative cases with a PTR <2·0 survived except for four patients who developed significant hypotension intraoperatively and a patient with a PTR of 1·5 who suffered no intraoperative hypotension but died on the general ward 3 weeks later from a massive rebleed. There were two patients with a PTR <2·0 who survived despite sustaining intraoperative hypotension. All ten operative ICU patients with a PTR >2·0 died with or without significant hypotension. In *Figure 2* it can be seen that significant hypotension occurred only in the three non-survivors whereas among the survivors it was not recorded. One of the patients who succumbed had a PTR <2·0; the other two who died had a very deranged PTR. Out of the total of 39 ICU patients none survived with a PTR ⩾2·2.

During the same period of 30 months, 46 patients bleeding from oesophageal varices and two bleeding from gastric varices were managed entirely on the general wards. The two gastric

Table 2 *Causes of cirrhosis of the liver in 39 intensive care unit patients with acute bleeding oesophageal varices*

	n	%
Hepatitis B	15	38
Schistosomiasis	9	23
Alcohol	1	3
Haemochromatosis	1	3
Cryptogenic	13	33
Total	39	100

Table 3 *Differences between survivors and non-survivors following acute bleeding oesophageal varices*

Variables	Survivors	Non-survivors	*P*
Operative cases			
Number of patients	13	15	
Encephalopathy present	1	4	
Hypotension	2	11	
Day 1 APACHE II score	14·6 (3·3)	22·5 (9·5)	<0·01
Risk of death	19·6 (10·0)	43·2 (26·3)	<0·01
Mean APACHE II BP score	1·7 (1·3)	2·3 (1·5)	n.s
Probability of discharge	0·81 (0·15)	0·35 (0·35)	<0·001
PTR	1·54 (0·20)	2·1 (0·4)	<0·001
Creatinine (μmol/l)	74·5 (30·9)	92·7 (33·6)	n.s
Units of blood	10 (7)	31 (12)	<0·001
Non-operative cases			
Number of patients	8	3	
Encephalopathy present	2	1	
Hypotension	0	3	
Day 1 APACHE II score	13·8 (5·0)	22 (5·3)	<0·05
Risk of death	28·6 (13·8)	66·2 (4·4)	<0·005
Mean APACHE II BP score	0 (1·0)	3·3 (1·2)	<0·01
Probability of discharge	0·5 (0·4)	0·1 (1·2)	n.s
PTR	1·7 (0·3)	2·5 (0·5)	<0·01
Creatinine (μmol/l)	104·5 (56·4)	215·5 (70·9)	<0·025
Units of blood	11 (10)	10 (4)	n.s

Standard deviations are shown in parentheses, PTR, initial prothrombin time ratio, n.s., not significant, BP, blood pressure

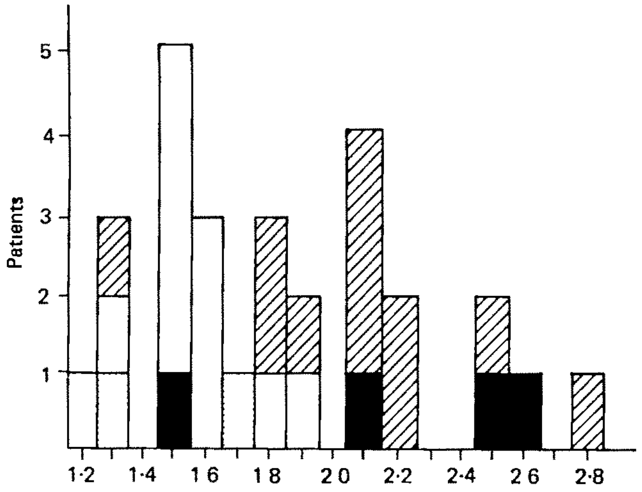

Figure 1 *Outcome of operative intensive care unit patients with acute variceal haemorrhage in relation to initial prothrombin time ratio and significant intraoperative hypotension (SIH).* □, *Alive and no SIH;* ▨, *alive and SIH;* ■, *dead and SIH;* ■, *dead and no SIH*

variceal patients had stapling of their gastric varices and splenectomy surgery for control of their bleeding. They could not be accommodated in the ICU because of an acute shortage of beds. Their PTRs were 1·0 and 1·9. They both survived their hospital stay. All the remaining 46 patients with bleeding from oesophageal varices were treated by sclerotherapy only and did not undergo surgery. Among these 48 ward-treated patients the mortality was 10 per cent (5/48). The male to female sex incidence within this ward-treated group was 8·8.1. The incidence of schistosomiasis, hepatitis B virus, cryptogenic and alcoholic-related chronic liver disease within these 48 ward-based patients was 50, 33, 12 and 4 per cent respectively. The mean age was 54·5 years (s.d. 11·3) which was not significantly different from that of the ICU patients The mean PTR of survivors was 1·43 (s.d 0·35) and of non-survivors was 4·03 (s.d. 2·89, $P<0\cdot005$). No patient within this series survived with a PTR $\geqslant 2\cdot2$ except for one patient with a PTR of 2·5 who was transferred elsewhere for liver transplantation.

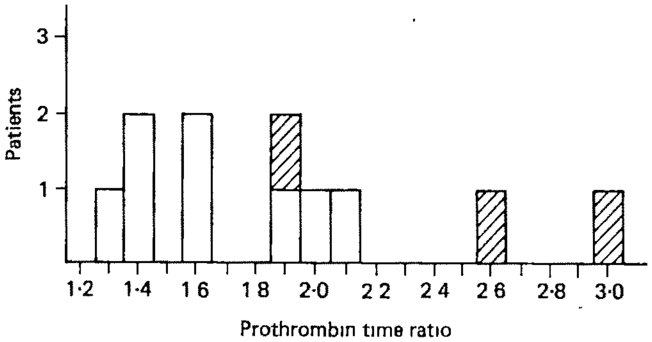

Figure 2 *Outcome of non-operative intensive care unit patients with acute variceal haemorrhage in relation to initial prothrombin time ratio and significant day one hypotension (SH).* □, *Alive and no SH;* ■, *dead and SH*

Table 4 *Predicted and actual outcome for 87 patients with variceal haemorrhage*

	Predicted to live	Predicted to die	Total
Actual alive	63	1*	64
Actual dead	8	15	23
Total	71	16	87

Sensitivity	65 per cent
Specificity	98 per cent
Predictive value of dying	94 per cent
Predictive value of living	89 per cent
Proportion correct	90 per cent

* This patient underwent successful liver transplantation The predictive criterion is a prothrombin time ratio of $\geqslant 2\cdot2$

The predictive power of a PTR value of 2·2 in all the patients is shown in *Table 4*. The predictive value for dying among the 87 patients using this criterion was 94 per cent.

Discussion

Our overall hospital mortality rate from acute variceal bleeding in this series was 26 per cent (23/87) whereas the mortality rate of the 30 operative patients (50 per cent) was more than triple that of the 57 non-operative patients (14 per cent). The mortality rate of 46 per cent (18/39) among the ICU patients is within the range expected in that group of patients with acute variceal haemorrhage who require emergency surgery for control of their bleeding or who have failed to settle on sclerotherapy[3] Among the 39 ICU patients the mortality rate of the operated cases was 54 per cent, which is in close agreement with that quoted elsewhere[9] in patients bleeding from gastric varices; and of non-operated cases it was 27 per cent. The high operative mortality rate occurred despite the fact that the severity of illness, as assessed by the mean APACHE II risk of death, was greater in the non-operative group both in survivors and non-survivors, although this did not reach statistical significance. This is not surprising. As Murray and Macsween[10] have noted in the perioperative period, surgery *per se*, anaesthesia, blood loss, metabolic disturbances, and increased risk from infection may combine to precipitate hepatic failure in patients with chronic liver disease and thus fatally compromise recovery in these delicately balanced patients. In contrast the mortality rate of the 48 patients managed on the general wards was only 10 per cent. This group comprised 46 non-operative cases with bleeding oesophageal varices and two operative cases with bleeding gastric varices.

The ICU non-survivors had significantly higher mean APACHE II scores and risks of death than survivors indicating that they generally had a greater severity of illness. In fact five (28 per cent) of the total of 18 patients who died, three operative and two non-operative patients, had admission APACHE II scores >35 and were predicted to die on day 1 of ICU admission[6]. Prediction of death was not acted on in this study.

We have been able to validate the Glasgow predictor in our operative ICU patients but not in the non-operative ICU patients We have shown that the use of the initial PTR is a useful predictor in our population. All patients in this series with a PTR $>2{\cdot}2$ died with the single exception of a patient with alcoholic cirrhosis and an initial PTR of 2·5. He had a successful liver transplant. Using the criterion of 2·2 we were able to demonstrate a specificity of 98 per cent These data confirm our clinical impression that in patients with known chronic liver disease and markedly deranged liver function, as exemplified by a grossly elevated PTR (i.e. $>2{\cdot}0$), surgery should be avoided if at all possible It should be noted that our patients differed from those in Glasgow[4] in that we had less alcoholic cirrhosis (3 per cent as opposed to 70 per cent), but more cirrhosis due to hepatitis B virus (36 per cent as opposed to 7 per cent) and schistosomiasis did not feature in the Glasgow material while it accounted for portal hypertension in 38 per cent of our patients.

The reason that our mortality rate was so strongly associated with the PTR may be related to the fact that many of our patients had some form of postnecrotic cirrhosis, most of these patients show a disturbance of coagulation. Lewis *et al.*[11] have pointed out that the severity of bleeding in liver disease does not necessarily correlate with the extent of the coagulation defect. Furthermore, not all patients with advanced liver disease develop coagulation abnormalities or bleeding Thus our results should be extrapolated with caution to other populations, although they may well be applicable to other regions in the Middle East and Africa.

An incidence of bleeding gastric varices of 34 per cent among our patients is at the higher end of the range of the incidence of 3 per cent to 30 per cent reported in other series[9,12,13]. This may partly be due to the high incidence of schistosomiasis in our population which was 30 per cent (9/30) among the patients with bleeding gastric varices

This study has re-emphasized the important observation that any significant hypotensive episode will further compromise outcome in these very sick patients. The effects of hypotension are presumably due to a reduction in hepatic arterial flow from vasoconstriction and reduction in portal blood flow from reduced splanchnic perfusion. The injury is known to affect the perivenular hepatocytes[14] which undergo coagulative necrosis[15]. It is thus vitally important that if patients with known chronic liver disease require emergency operative intervention for whatever reason their blood pressure is maintained as close to normal levels as possible; all strategies directed at improving splanchnic blood flow will be very important.

We are currently testing the PTR criterion of 2·2 for patients with proven chronic liver disease and portal hypertension to ascertain if it is capable of differentiating survivors from non-survivors with a specificity of 100 per cent (i e. all patients who are predicted to die, die). Validation of the predictive power of this criterion may guide us in the future to identify those patients whose probability of survival is so poor that active treatment in the ICU or surgical intervention, without the possibility of liver transplantation, should be discontinued. This will save valuable operating time, avoid unnecessary demands on skilled personnel in theatre and the ICU, and reduce the massive drain of blood and blood products from the blood bank for use in patients who have no prospects for survival.

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Anastomotic leakage: an avoidable complication of Lewis–Tanner oesophagectomy

I. M. Paterson and J. Wong

Department of Surgery,
University of Hong Kong,
Queen Mary Hospital,
Hong Kong
Correspondence to:
Professor J. Wong

Data were collected prospectively from 159 patients undergoing Lewis–Tanner oesophagectomy for carcinoma of the lower two-thirds of the oesophagus and analysed with regard to anastomotic leakage. The 30-day mortality rate was 3·8 per cent and none of these deaths was due to anastomotic leakage. In hospital, mortality was 7·5 per cent. Six patients (3·8 per cent) had evidence of a leak. In four patients this was from the suture line, but in the remaining two it was due to patches of gangrene in the fundus of the transposed stomach and was separate from the anastomosis. Two patients died with an unhealed leak. Anastomotic leaks were minor in three instances and healed with conservative treatment but the fourth required exploration. Gangrene of the oesophageal substitute resulted in gross leakage with mediastinitis and required exploration in both cases. An apparent predisposing cause was evident in five of the six cases with leakage and some of these might have been avoidable. Transthoracic oesophagectomy can be performed with acceptably low mortality and leak rates and may therefore be considered as the treatment of choice for most patients with oesophageal cancer.

Keywords: Oesophageal neoplasm, oesophagectomy, anastomotic leakage

The prognosis of patients with carcinoma of the oesophagus is poor but treatment can provide useful palliation by restoring the ability to swallow. It is also possible to achieve 5-year survival rates of 43–54 per cent in those patients who have had resections for node negative disease[1–3]. There is, however, a widespread reluctance to submit patients to oesophageal resection because of the reported high mortality rate from many series: 20 and 33 per cent in two large reviews[4,5] respectively with the major complications being cardiorespiratory problems and anastomotic leakage. As a result many patients are treated by radiotherapy, intubation or laser which achieve inferior palliation and are attended by either less or no chance of cure. There is also controversy about the type of approach that should be used for oesophagectomy and there has been a recent trend towards transhiatal oesophagectomy without thoracotomy. It has been our preference to treat carcinoma of the middle and lower thirds of the oesophagus by oesophagectomy and oesophagogastric anastomosis using a laparotomy and right thoracotomy approach as first described by Lewis[6] and by Tanner[7]. The purpose of this paper is to highlight the low anastomotic leak rate and mortality rate which can be achieved with this type of oesophagectomy and to analyse the predisposing causes of those leakages which did occur.

Patients and methods

Between July 1982 and April 1987, data were collected prospectively from 364 unselected patients with carcinoma of the middle and lower thirds of the oesophagus who were admitted to the Department of Surgery, University of Hong Kong at Queen Mary Hospital All patients underwent surgery unless they were in the terminal stages of the disease or refused operation. The preferred method of resection and reconstruction was the Lewis–Tanner oesophagectomy which had been modified so that the oesophagus was resected to the apex of the thorax[8]. Transhiatal oesophagectomy was reserved for patients with diminished pulmonary reserve Colon or jejunum was only used as the oesophageal substitute when the stomach was diseased or had previously been resected The 159 patients who had a Lewis–Tanner oesophagectomy form the basis of this study. There were 141 men and 18 women with a mean age of 60 years Only one tumour was an adenocarcinoma, the remainder being squamous carcinomas. Seventy-eight patients (49 per cent) were considered to have had a potentially curative resection while 81 (51 per cent) had the resection for palliation only.

At operation, an upper midline abdominal incision was used and the stomach completely mobilized preserving whenever possible the right gastric as well as the right gastroepiploic vessels. Seventy-nine of the patients had a pyloroplasty, three had pyloromyotomy and 77 had no gastric drainage procedure. Right thoracotomy was then performed through the fifth interspace and the oesophagus resected together with a mediastinal node dissection. Distally the stomach was transected just below the cardia while the proximal line of transection was at the apex of the right chest An oesophagogastric anastomosis was made between the oesophagus and the posterior wall of the fundus of the stomach A circular stapler was used if possible and the largest size which would fit into the oesophageal lumen was chosen[9] An EEA stapler (US Surgical Corporation and Auto Suture UK, Ascot, UK) was used in 62 cases and an ILS stapler (Ethicon Ltd , UK) in 88 cases Nine patients had an anastomosis performed with a single layer of continuous, absorbable suture when the oesophagus was too small to admit a stapler.

Radiological contrast swallows were not routinely performed since an earlier study showed them to be of no clinical value and potentially dangerous[9] We have, however, adopted an aggressive approach towards excluding leaks in patients who have evidence of sepsis. If a leak was suspected,then a Gastrografin (Schering AG, Berlin, FRG) swallow or endoscopy was used to establish the diagnosis In two cases thoracotomy was performed without prior confirmation of a leak because there was evidence of severe mediastinal contamination

Results

Of the 159 patients in this series, six (3·8 per cent) died within 30 days of the operation but none of these deaths was related to anastomotic leakage. Another six patients died up to 5 months after their operation without being discharged from hospital giving a total hospital mortality rate of 7·5 per cent. The causes of death in these patients were: bronchopneumonia (three), anastomotic leakage (one), septicaemia due to subphrenic abscess (one) and cerebral metastasis (one).

Six patients (3·8 per cent) had evidence of leakage. In four of the patients the leakage was from a staple or suture line but in the other two the defect resulted from a patch of gangrene in the fundus of the stomach which was separate from the anastomosis.

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A predisposing cause could be identified in each of the four patients with an anastomotic leak. Two of the patients required a thoracotomy for postoperative bleeding within 2 days of their oesophagectomy. One patient who did not have a gastric drainage procedure developed gastric outlet obstruction with gastric distension before the leak became apparent. In the fourth patient the leak was not directly from the oesophagogastric anastomosis but from a longitudinal tear in the oesophagus above the line of resection This had been recognized and repaired at the original operation and was attributed to rigid oesophagoscopy performed immediately before the operation. In three of the patients the leak produced minor evidence of sepsis (pyrexia $<38°C$, no evidence of pleural effusion or shock) and the diagnosis was made endoscopically. These were treated conservatively and healed. The fourth patient required exploration and drainage, healing did not occur and the patient died 33 days postoperatively.

Both patients who had patches of gangrene in the fundus of the stomach developed clinical features of gross mediastinal contamination with high fever, hypotension and pleural effusion. Thoracotomy was performed for pleural toilet, to establish drainage and to attempt repair of the defect, but this was unsuccessful in one and the leak persisted until the patient died 5 months later The latter patient had required a laparotomy for small bowel herniation into the chest 2 days after oesophagectomy and had a period of hypotension at this time

The development of leakage did not appear to be related to the method of anastomosis chosen: three by EEA stapler, two by ILS stapler and one by hand. None of the six patients received preoperative radiotherapy

Discussion

Oesophagectomy can only be considered a useful form of treatment for carcinoma of the oesophagus if the morbidity and mortality rates of the procedure are low. There is also controversy about the type of oesophagectomy and anastomosis that should be employed in order to minimize these risks. A major disadvantage of transthoracic oesophagectomy in the past has been the high mortality rate which was largely due to anastomotic leakage. This was highlighted in the review by Earlam and Cunha-Melo who reported an overall mortality rate of 33 per cent[5]. Recently, much improved mortality figures have been reported which might be attributable to the very low anastomotic leak rates (0–3·5 per cent) that can be obtained with the circular stapler[10–13] Good results have also been obtained with a sutured anastomosis. Akiyama *et al.*[3] have reported a mortality rate of 1·4 per cent and a leak rate of 5·2 per cent, while Huang *et al.*[2] in a large study of 1647 cases were able to achieve mortality and leak rates of 4·1 and 4·5 per cent, respectively. A previous report from this unit failed to show any difference in leakage between an anastomosis by hand and by stapler, although the latter produced a higher incidence of postoperative stricture[9]. The anastomotic leakage rate of 2·5 per cent and overall leak rate of 3·8 per cent in the present series compares favourably with those quoted above despite an aggressive policy of surgical treatment—76 per cent of unselected patients underwent operation and 63 per cent had a resection.

One of the stated advantages of transhiatal over transthoracic oesophagectomy is that, given a high anastomotic leak rate, the consequences of a leak in the neck are less than in the mediastinum. However, this becomes relatively unimportant if the incidence of anastomotic leakage is low. Since the proximal line of resection is similar in the two methods if the oesophagus is resected transthoracically to the apex of the chest[8], the major differences remaining between the two approaches are the relative risk of postoperative cardiorespiratory problems, and the merits of performing a blind or visualized mediastinal dissection. Argument regarding the first point is unresolved, although one non-randomized comparison has suggested that it may be higher after transhiatal oesophagectomy[14]. The risk of uncontrolled bleeding or bronchial damage using the transhiatal approach is considerable[15] and the incidence of mediastinal recurrence high[16]. We feel therefore that the present trend towards the use of the transhiatal route in most cases is not justified.

Analysis of those leaks which did occur in the present series reveals that the majority may have been avoidable. Two patterns of leakage are evident. those characterized by suture or staple line dehiscence and those due to gangrene of the oesophageal substitute Of the four patients who leaked from a suture line all had a possible predisposing cause. One was unusual in that the leakage occurred from the site of oesophageal perforation following preoperative rigid oesophagoscopy and this resulted in the only death due to an anastomotic leak. The three other cases were diagnosed endoscopically and since they were minor were treated conservatively with a successful outcome. Hypotension and haematoma around the anastomosis may have been precipitating factors in the two patients who required an emergency thoracotomy for bleeding within 2 days of their oesophagectomy. A prolonged period of postoperative gastric distension may have resulted in the fourth leak by putting excessive tension on the anastomosis A gastric drainage procedure had not been performed but the use of this as routine after oesophagectomy has been controversial. The morbidity associated with a pyloroplasty however is low and since it is impossible to predict accurately which patients will have delayed gastric emptying postoperatively it may be safer to do this in every case[17].

The distinction between anastomotic leakage and ischaemia of the oesophageal substitute may be a fine one but differences in the degree of contamination and hence clinical presentation and type of treatment required are evident. Both patients with gangrene of the stomach in this series developed mediastinitis. When the area of necrosis is large, resection of the substitute with cervical oesophagectomy and feeding gastrostomy or jejunostomy will probably be required. However, if the area of necrosis is limited, excision and repair may occasionally be possible but selection of these cases is important—primary repair was attempted in both our patients but was successful in only one. The distinction also emphasizes the need to preserve a good blood supply to the oesophageal substitute and to avoid episodes of hypotension or hypoxia, particularly in the early postoperative period. Such a predisposing cause was identified in one of the two patients since there was a period of hypotension before emergency laparotomy 2 days after oesophagectomy.

There are conflicting views as to the measures which should be taken to preserve the blood supply to the transposed stomach. All authors agree that the right gastroepiploic vessels must be preserved. The right gastric vessels can probably be divided at their origin in the majority of cases but the risk of this has not been quantified and our own practice is to preserve them if possible. Akiyama[18] leaves the antral portion of the right gastric artery, excising the first three branches of the left gastric artery with the proximal half of the lesser curvature, but stresses the importance of preserving the intramural vascular network. McKeown[19], however, feels that the entire vascular system along the lesser curve should be kept intact and therefore ligates and divides the left gastric artery flush at its origin. There is no firm evidence to favour any one of these practices.

In conclusion, on the basis of these results it would appear that anastomotic leakage may be largely an avoidable complication and the overall mortality rate in the present series was low, further improvement should be the goal.

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Case report

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Chylothorax and delayed paraparesis in an infant following improper use of a front seat belt

J. H. E. Laing and L. Spitz

Hospital for Sick Children, Great Ormond Street, London, UK

Correspondence to: Mr H. Laing, Department of Surgery, Orthopaedic Surgery, Brook General Hospital, London SE18, UK

Traumatic chylothorax and spinal cord injury due to blunt trauma are both very uncommon lesions in infants[1-3]. Such a case, following the incorrect use of a car seat belt, is reported.

Case report

A healthy 7-month-old male infant was being breast-fed in the front passenger seat of a motor car. The child was held inside the diagonal strap of the seat belt, which lay across his right chest and back. The front of the car struck a stationary vehicle at approximately 60 m.p.h. Mother and child were thrown forwards against the seat belt.

There was no loss of consciousness but the child became pale and cyanosed and, on admission to hospital, was cold, tachycardic and hypotensive (BP 40/20 mmHg). Chest X-ray showed a left-sided pleural effusion and 100 ml of blood was aspirated. Following resuscitation with blood and plasma he was able to commence breast-feeds.

Within 8 h he developed progressive respiratory embarrassment. A further 50 ml of blood was aspirated from the left pleural cavity and 75 ml of milky fluid from the right pleural cavity. Examination revealed signs of recurrent bilateral pleural effusions, but there was no evidence of intra-abdominal injury and a full neurological examination was normal. Bilateral basal chest drains were inserted, the left draining bright red blood, the right draining chyle (triglyceride 19·5 mmol/l). He was intubated and positive pressure ventilation instituted. Total parenteral nutrition (TPN) was commenced using a standard regimen. His condition improved and mechanical ventilation was discontinued on the fourth day, at which time medium chain triglyceride feeds were introduced. TPN was discontinued 24 h later, as the chylous effusion had reduced to minimal volumes.

Six days after admission he developed bilateral flaccid paraplegia but with retention of normal anal and bladder tone. X-ray of the cervical, thoracic and lumbar spine and computerized tomography of the brain and cervical spine were normal.

A myelogram showed no evidence of spinal cord compression, but there was leakage of contrast medium from the theca at D8–10 level. The contrast medium filled a widened epidural space on the left and leaked out through the intervertebral foramina (*Figure 1*).

Medium chain triglyceride feeds were continued for 2 weeks after which breast-feeding was restarted. There was no reaccumulation of the chylothorax. Six months after the injury he has regained partial use of his lower limbs and is otherwise well.

Discussion

Right-sided traumatic chylothorax, in the absence of bony or penetrating injury, is very uncommon and is probably due to the shearing action of the right crus of the diaphragm acting upon a thoracic duct which was distended following a fatty meal[4]. Just above the diaphragm the duct lies on the anterior surface of the vertebral column posterior to the oesophagus, and the likely mechanism of injury is hyperangulation of the spine[5].

The use of parenteral nutrition and medium chain triglyceride feeds in the management of chylothorax is based on the observation that while long chain fatty acids are absorbed into the intestinal lymphatics and hence into the thoracic duct to form chyle, short and medium chain fatty acids pass directly into the portal circulation[6]. It is occasionally necessary to ligate the duct at the diaphragm if conservative management fails[7].

The paraplegia observed in this child is most unusual and was probably associated with the dural tear observed on the myelogram. Spinal cord injury in children may occur without any associated vertebral injury. The delay in onset of neurological signs in the absence of spinal cord compression is suggestive of an ischaemic aetiology[8]. It is noted that the arteria radicularis magna (of Adamkiewicz) enters the cord close to the level of the dural tear. This vessel arises from the lower left intercostal vessels in 80 per cent of cases, and damage to these vessels may result in ischaemic paraplegia[8,9]. Longitudinal

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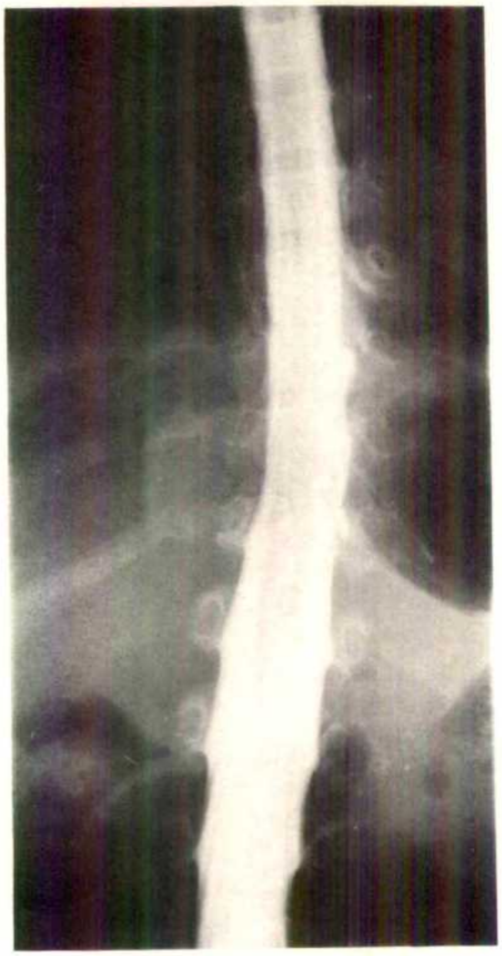

Figure 1 *Myelogram showing leakage of contrast medium from dura, and the position of the artery of Adamkiewicz*

traction to the spinal cord can cause infarction of the conus in this manner[7,8].

We postulate that hyperangulation of the lower thoracic spine over the seat strap resulted in a tear in the thoracic duct on the right causing chylothorax, and an avulsion injury to the artery of Adamkiewicz or its tributaries on the left causing an ischaemic cord injury.

The use of seat belts has been shown to reduce the severity of injury to adults in motor vehicle accidents, and the use of approved child restraints to reduce child mortality[10]. Following legislation in 1983 enforcing the use of front seat belts, over 95 per cent of adults now comply. Since only 25 per cent of the population use child restraints, the illegal carriage of children inside front seat belts with adults is probably common, and in the event of an accident may result in severe injuries to the child[11]. The risks should be widely publicized, and the use of approved child restraints encouraged.

Acknowledgements

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Gastroplasty for morbid obesity: technique, complications and results in 60 cases

E. R. T. C. Owen,
R. Abraham* and
A. E. Kark

Departments of Surgery and
**Dietetics, Northwick Park Hospital*
and MRC Clinical Research Centre,
Harrow, Middlesex, UK

Correspondence to:
Mr E. R. T. C. Owen, Academic
Surgical Unit, St. Mary's Hospital,
Praed Street, London W2 1NY, UK

A series of 60 gastroplasty operations based on Mason's vertical banded procedure are described. Details of technique, modifications, complications and results are discussed. Operative treatment results in a reduction to within 40 per cent of ideal weight in 80 per cent of patients between 12 and 18 months after surgery. The constricting band should not be greater than 5 cm; if it is most procedures will fail after 18 months. Pouch size should be measured and made no greater than 20 ml. The importance of nutritional counselling is emphasized. The surgical treatment should form part of a multidisciplinary approach with careful selection and long-term follow-up.

Keywords: Gastroplasty, morbid obesity, surgical technique, complications, weight loss, band size

Gastric reduction procedures have been shown to produce impressive short-term results in the treatment of morbid obesity[1,2]. Vertical banded gastroplasty or one of its modifications is the most widely used technique[3,4]. These stomach operations have almost entirely superseded small intestinal bypass operations which cause disabling metabolic disturbances[5]. While the single most obvious effect is weight reduction with its concomitant physical and social benefits, much less is understood about the causes of persistent severe obesity, the effects of gastroplasty on body composition[6], or the behavioural factors underlying gross overeating.

The earlier methods of gastroplasty failed largely because of pouch enlargement and inappropriate dietary supervision. We document here the results and complications in a series of 60 patients undergoing vertical banded gastroplasty with emphasis on the technical factors necessary for long-term successful weight loss and the importance of regular medical and dietary supervision to maintain long-term alteration in eating habits.

Patients and methods

Since 1983, 60 patients (aged 18–56 years, mean 38·8) have undergone vertical banded gastroplasty as a primary operation for weight loss (*Figure 1*). All had unsuccessfully attempted numerous dietary and group therapy regimens. All were morbidly obese, i.e. they were either at least twice ideal body-weight or more than 45 kg overweight, having been so for 5 years or more, and all suffered the debilitating morbidity of gross obesity.

All patients demonstrated the triad of symptoms: joint pain (back, hip and knee), increasing breathlessness after minimal physical exertion, and increasing social and psychological disabilities. In addition many complained of biliary symptoms, early diabetes, hypertension, loss of energy and depression. More rarely sleep apnoea occurred[7,8]. We relied on an experienced nurse counsellor, a dietitian and a lay support group to act as an additional screen to assess the stability of family background and the less easily defined attributes of perseverance and motivation. Any tendency to alcoholism or past psychiatric disorders was considered an absolute contraindication to surgery.

All patients underwent routine haematological and biochemical studies, liver function assessment and gallbladder ultrasound, chest X-ray, ECG and comprehensive pulmonary function tests, including arterial blood gas levels. In addition most patients underwent preoperative upper gastrointestinal barium studies and/or endoscopy.

Operative technique

The technique to be described was used in all patients except that: (a) the pouch size was estimated in the first 24 cases and then accurately measured in the last 36; and (b) the outlet band was initially 5·5 cm Marlex® (C.R. Bard Inc., Massachusetts, USA) but in the past 2 years a 4·5 cm or 4·75 cm GORE-TEX® (W. L. Gore and Associates Ltd., UK) band has been used (see Discussion).

Subcutaneous heparin and an H_2 receptor antagonist were administered with the premedication and a peroperative broad-spectrum antibiotic was given. Through an upper midline incision the fat is split by manual traction. A Goligher frame retractor is essential and we have designed a set of special rib retractors attached to it[9]. The oesophagogastric junction is mobilized and taped. The lesser sac is opened, all adhesions to the pancreas up to the level of the oesophagus are divided and the posterior margin of the lesser curve cleared along its length. The lesser omentum is opened at this level hard against the lesser curvature to avoid vagus and venous branches. A large 32 Ewald tube is passed into the stomach by the orogastric route. A point is marked 5 cm down from the oesophagogastric junction and 5 cm in from the medial edge of the lesser curve by a Babcock forcep. At this point a Hearn needle[10] attached to the EEA instrument (Auto Suture Company, Ascot, UK) is pushed through both walls of the stomach. The EEA instrument is positioned so that the rim of staples abuts against the tube, and is closed to excise and staple a 28 mm window which is then oversewn with a 2/0 linen continuous suture. A linear stapler (55, 60 or 90 mm) is then passed through the window to emerge at the oesophagogastric junction and positioned to lie parallel to the lesser curve. After temporary closure of the stapler the Ewald tube is withdrawn into the lower oesophagus and a fine-bore nasogastric tube is introduced; two soft enterostomy clamps are placed, one across the oesophagogastric junction and the other across the distal opening of the pouch (*Figure 2*). The aim is to create a pouch with 10–20 ml capacity at a pressure of 25 cmH_2O by adjusting the position of the

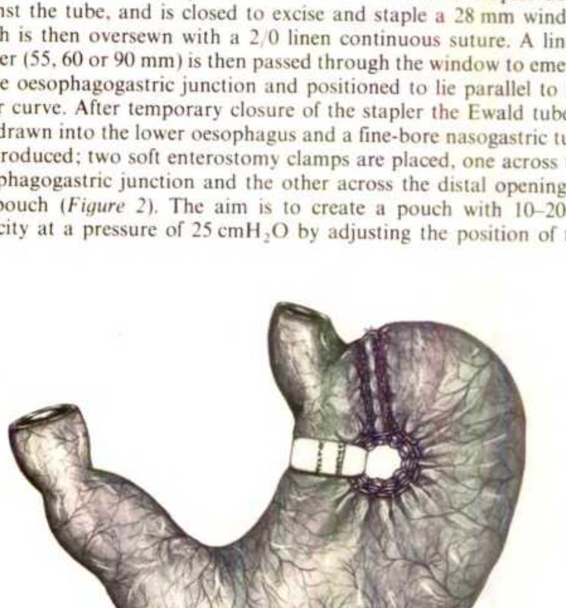

Figure 1 *Completed vertical banded gastroplasty (adapted from Flejou* et al.[25])

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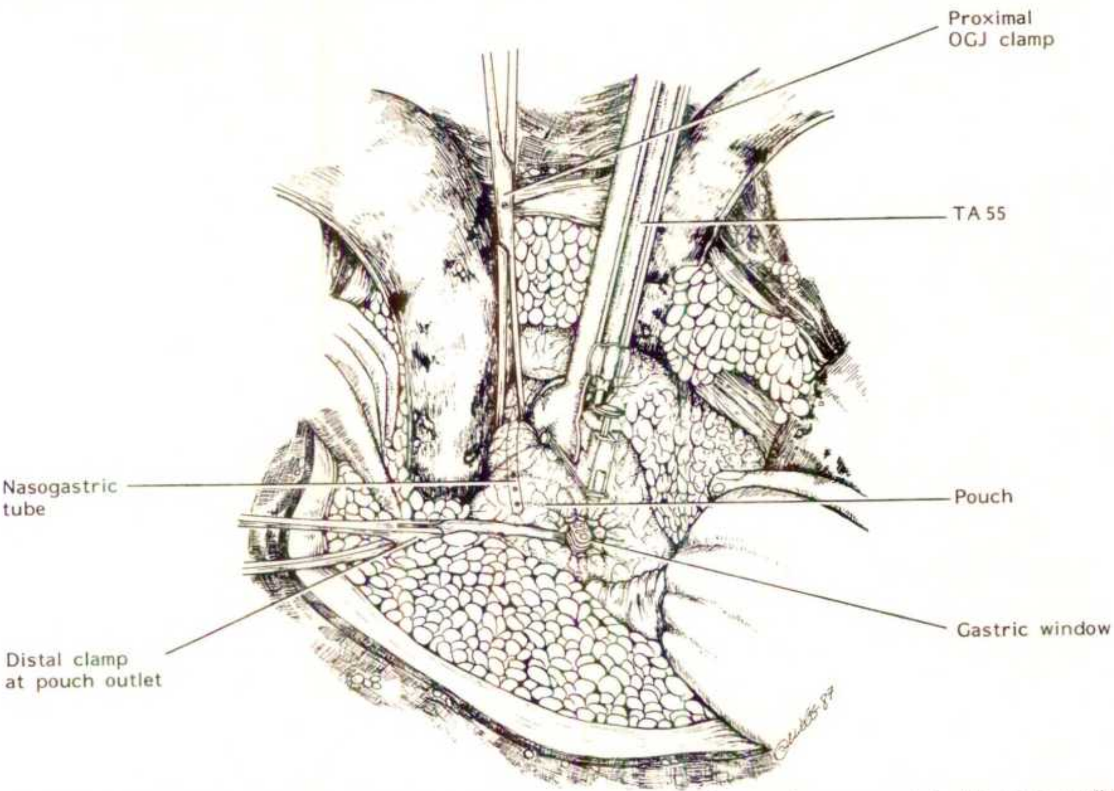

Figure 2 *Position of the stapler and nasogastric tube with enterostomy clamps in place before pouch measurement. In this case a small linear stapler has been passed downwards from the oesophagogastric junction so that the anvil emerges through the window. TA55 is manufactured by US Surgical Corporation and Auto Suture Company UK, Ascot, UK*

stapler. The staples are then fired using a double cartridge with four staple lines or two parallel applications of a single cartridge. The staple line is reinforced anteriorly by silk sutures to prevent strain and separation of the staple line (*Figure 1*). The integrity of the pouch is tested by instilling methylene blue via the narrow nasogastric tube with two soft clamps in place (*Figure 2*). A 6 cm strip of GORE-TEX 1·5 cm wide is placed around the pouch exit (*Figure 1*) so that 1·25 cm overlaps making a 4·75 cm circumference band. This is fixed by interrupted GORE-TEX sutures with the large Ewald tube in place to avoid narrowing. Omentum is brought over to cover the GORE-TEX. Cholecystectomy is then done if deemed necessary. Abdominal closure is secured by one layer of looped continuous No. 1 monofilament nylon followed by subcuticular Prolene® (Ethicon Ltd., Edinburgh, UK). The peritoneal cavity is not drained and no nasogastric intubation is used.

The patient is extubated in a sitting position, which is maintained in a chair during the first 6–8 h postoperatively. Chest physiotherapy and mobilization is started immediately and repeated two or three times a day, and a subcutaneous morphine pump infusion (2–5 mg/h) provides adequate analgesia and allows good lung expansion. The first 31 patients were managed in the intensive care unit postoperatively for 24 h. This has been found to be unnecessary and patients are returned to the ward where nursing staff are familiar with the procedure.

H_2-receptor antagonists are given intravenously and then orally after day 1, and subcutaneous heparin is continued until full mobilization after 4–5 days. Fluids are encouraged from the first day and small amounts of purées by days 2–3. Discharge is arranged by the fifth or sixth day and sutures removed later as an outpatient. Within the early postoperative weeks a barium study is done to provide a baseline measurement of the size of the gastric pouch and outlet.

Postoperative dietary management must ensure a 3200 kJ nutritional intake which permits a safe weight loss[11]. Full fluids are continued for 4–12 weeks including small quantities of soup, jelly and drinks. When purées are started a pint of skimmed milk per day is recommended to provide the appropriate energy intake. A mineral and vitamin supplement makes up the nutritional deficit that has been demonstrated on these diets[12,13]. Solids are slowly introduced after 2–3 months and it is largely texture and not quantity that alters at this stage.

Statistical methods

Body-weight was expressed as a percentage of the ideal weight. Ideal weight was taken as the maximum weight for height and calculated using Quetelet's index ($\text{weight} \div \text{height}^2 = 25$). Patients were assessed and weighed at regular intervals postoperatively: monthly for the first 6 months, 3-monthly for the next 6 months, and 6-monthly after this. At 6-monthly intervals the change in the percentage ideal body-weight was calculated. For each 6-month postoperative period up to 2 years, an analysis of variance was performed to compare the mean change in this percentage for the four band sizes. A further comparison was done at 3 years. Weight changes after revision were excluded. The band size of 5·5 cm was then compared with the mean of the other three band sizes using the pooled estimate of standard deviation from the analysis of variance.

As the aim of any treatment for obesity is loss of the patient's excess weight we have used percentage excess body-weight to show the weight loss postoperatively (*Figures 3–6*). This is calculated by subtracting 100 from the percentage ideal body-weight and is the method recommended by a consensus of the American Society of Bariatric Surgeons for expressing the results of obesity surgery. There are no standard criteria for assessing the success of these operations in terms of weight loss but it is generally accepted that if the patient's weight reduces to a level within 40 per cent of their ideal weight (140 per cent ideal body-weight or 40 per cent excess weight) then most of the obesity-related health hazards will be circumvented and the operation can be considered a success, provided the weight loss can be maintained.

Results

Complications

Mortality. There were no hospital deaths but two patients died at home 40 and 45 days after operation. In both cases, death was due to autopsy-proven pulmonary embolus.

Gastric bleeding. Bleeding occurred in one case, requiring re-exploration of the stomach. No local lesion was found and the cause appeared to be widespread gastritis which responded to further conservative treatment and H_2-receptor antagonists.

Leaks. One leak was detected by methylene blue peroperatively and this was immediately repaired. There were no postoperative leaks.

Wound infection. Six patients (10 per cent) developed major wound infections and one developed wound dehiscence, 6 weeks

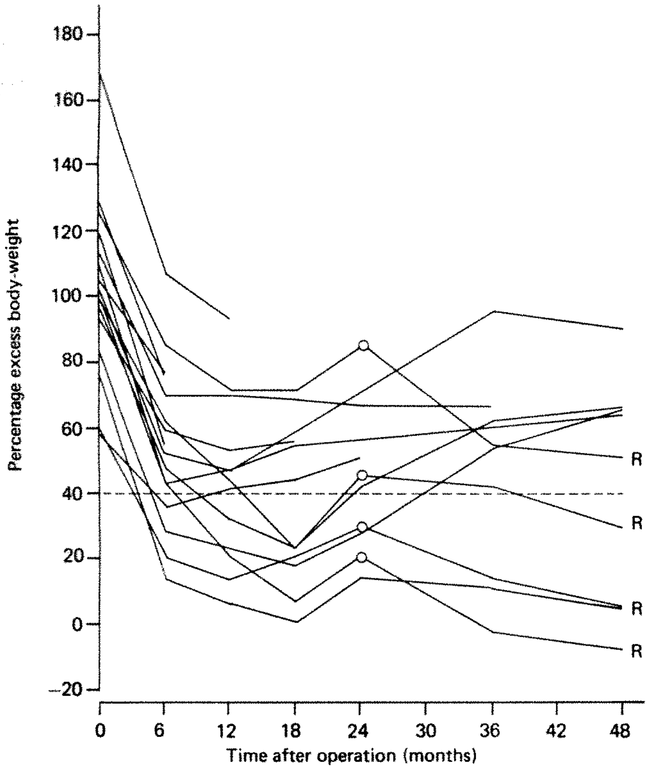

Figure 3 *Postoperative change in percentage excess weight up to 4 years in patients with a 5·5 cm band. Four patients underwent revision (R). The aim is for the patient to reduce weight so as to be within the 40 per cent (---) excess weight level (140 per cent ideal body-weight).* ○, *Revision date. One patient in this group died and is not included in the figure*

later while at home. Twenty-four (40 per cent) had minor serous discharge and 17 (28 per cent) of these had positive cultures (13 with *Staphylococcus epidermidis*). Concurrent cholecystectomy in nine patients resulted in one case of major sepsis. There has been one case of incisional hernia to date.

Thromboembolism. One patient developed venographically confirmed deep vein thrombosis and suffered a non-fatal pulmonary embolus, in addition to the two fatalities above.

Chest infection. There were eight cases (13 per cent) with purulent sputum and a positive culture. Six had mucopurulent sputum and a normal flora. Eight cases (13 per cent) of atelectasis were noted on X-ray but the patients were otherwise asymptomatic. Only one patient was electively ventilated for 24 h because of her shortness, kyphosis and extreme obesity.

Staple line dehiscence. Four patients (7 per cent) developed staple line dehiscence (diagnosed by barium meal and endoscopy), one at 6 weeks and the others after 1 year. Two of these patients had developed concomitant stomal stenosis (see below).

Stomal stenosis. Five patients (8 per cent) developed stenosis, one at 3 months and four after 1 year.

Band erosion. One patient developed band erosion 2 years after operation in which a Marlex band was used. This patient had a coexistent stomal stenosis and staple line dehiscence. She stabilized her weight after 6 months and maintained this for 2 years so that no further action has been taken.

Pouch size was estimated in the first 26 cases to be 30–50 ml; 17 had a band of 5·5 cm and nine a 5 cm band. The remaining 34 patients have had accurate volumetric pouch measurement of 10–25 ml. The outlet bands in this group were fashioned in three sizes: 4·5 cm (21 cases, mean pouch volume 16·4 ml, s.d. 5·4), 4·75 cm (12 cases, mean volume 18·1 ml, s.d. 4·4), and 5 cm (one case, volume 10 ml). The postoperative change in percentage excess weight for each patient is shown in *Figures 3–6*.

In the 5·5 cm band group (*Figure 3*) nine of the 17 patients have been followed for 4 years; four have needed revision because of significant weight regain owing to failure of gastric restriction, four are regaining weight and only one has stabilized at 20 per cent above ideal weight. The remainder have failed to attend follow-up. Thus nearly 50 per cent of this group are known to have failed in terms of their response to surgery.

In the 5·0 cm band group (*Figure 4*) eight of ten patients have stabilized to within 40 per cent of their ideal weight and have so far maintained this for 2–3 years postoperatively. One other patient in this group has stabilized to within 80 per cent of her ideal weight but this represents a loss of 50 per cent of her excess weight and she has maintained this with good effect.

In the 4·75 cm band group (*Figure 5*) 11 of 12 patients have lost weight; of these two stabilized by 12 months at 10 per cent and 30 per cent above ideal weight. Nine are still losing weight and one has failed having regained all her lost weight after 12 months due to total dietary non-compliance.

In the 4·5 cm band group (*Figure 6*) all patients have lost weight; most patients have been followed for between 12 and 18 months and 18 have stabilized. Eight have stabilized at or near ideal weight, five at a level of 20–40 per cent excess weight and three at 40–60 per cent excess weight. Two have regained a small amount of weight. One patient aged 56 weighing 153 kg (170 per cent excess weight) does not appear to have done well: in fact she has lost almost half her excess weight (50 kg) and her life has been transformed; she is active, mobile and able to function normally compared with her previous room-bound existence.

Statistical analysis

There were no significant differences in weight loss for patients with different band sizes at 6, 12 or 18 months postoperatively.

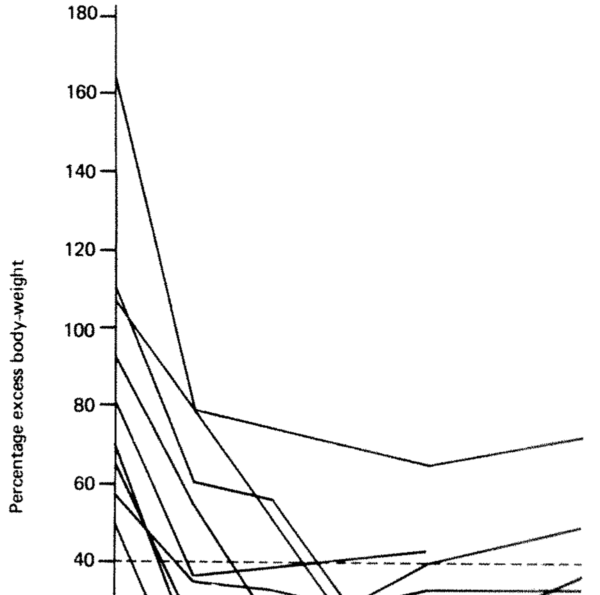

Figure 4 *Postoperative change in percentage excess weight up to 3 years in patients with a 5·0 cm band. ---, Forty per cent excess weight level. (One patient was lost to follow-up)*

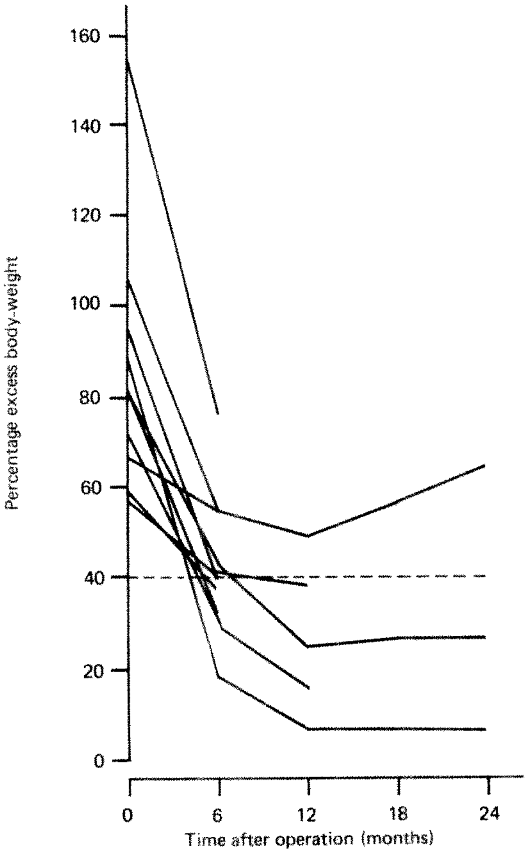

Figure 5 *Postoperative change in percentage excess weight up to 2 years in patients with a 4·75 cm band. ---, Forty per cent excess weight level. Two patients have not been included because postoperative follow-up was for <6 months*

However at 24 and 36 months the 5·5 cm band performed significantly less well than the other bands ($P = 0{\cdot}008$ and 0·05 at 24 and 36 months respectively). There was no significant difference between the 4·5, 4·75 and 5·0 cm bands at 24 and 36 months.

Figure 7 shows the change in percentage ideal weight during each 6-month period postoperatively. The mean and 95 per cent confidence intervals are shown for each band size. Zero represents no change in weight. Points above the zero line (minus figures) indicate weight loss and those below weight gain. Wherever the confidence interval for any 6-month period does not include the zero line there has been a significant gain or loss in the mean weight of the group. From *Figure 7*, it can be seen that patients with all band sizes lose a large amount of weight in the first 6 postoperative months. In the next 6 months all groups continue to lose weight but much more slowly. Weight stabilization occurs by 18 months. At 24 and 36 months the 5·5 cm band group regains weight (confidence intervals below and not including zero) whereas the other groups remain stable (confidence intervals include zero).

Discussion

The creation of a small proximal gastric pouch has been shown to be an effective method of weight reduction. The original method consisted of a horizontally stapled or sutured pouch with a Roux-en-Y or loop drainage. This constituted a major technical exercise with all the risks of gastrojejunal suture lines[14]. Thereafter a horizontally stapled pouch with a central or lateral gastrogastrostomy drainage stoma of 10 mm was developed[15], a much simpler technique which we adopted in a group of 20 morbidly obese patients. Within 18 months it was apparent that weight loss was unsatisfactory in the majority and the method was abandoned. The failure related directly to imprecise pouch size construction and continuing distension of an over-large pouch. Additionally the importance of regular

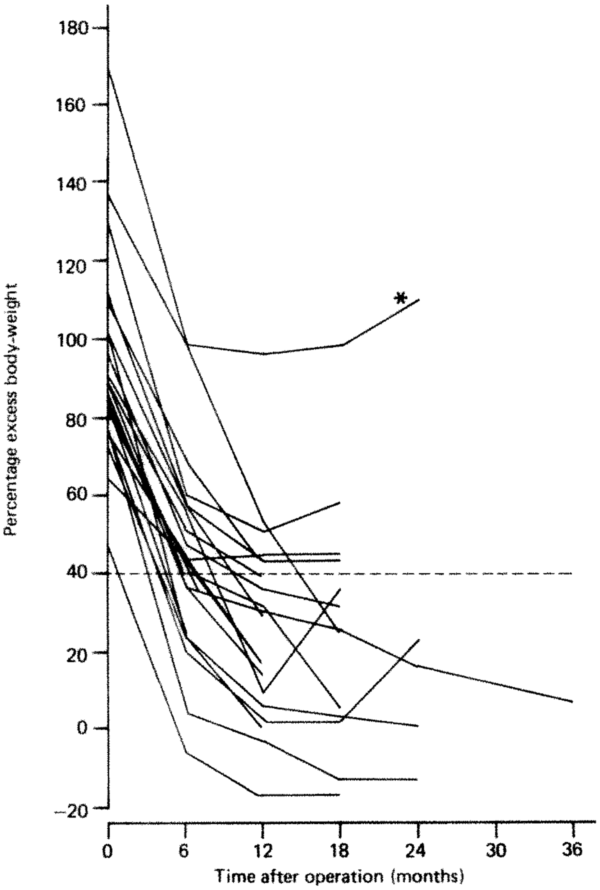

Figure 6 *Postoperative change in percentage excess weight up to 3 years in patients with a 4·5 cm band. ---, Forty per cent excess weight level. * A 56-year-old patient weighing 153 kg (170 per cent excess weight), who does not appear to have done well, in fact, lost half her excess weight and the operation was considered successful. One patient in this group died and is not included in the figure*

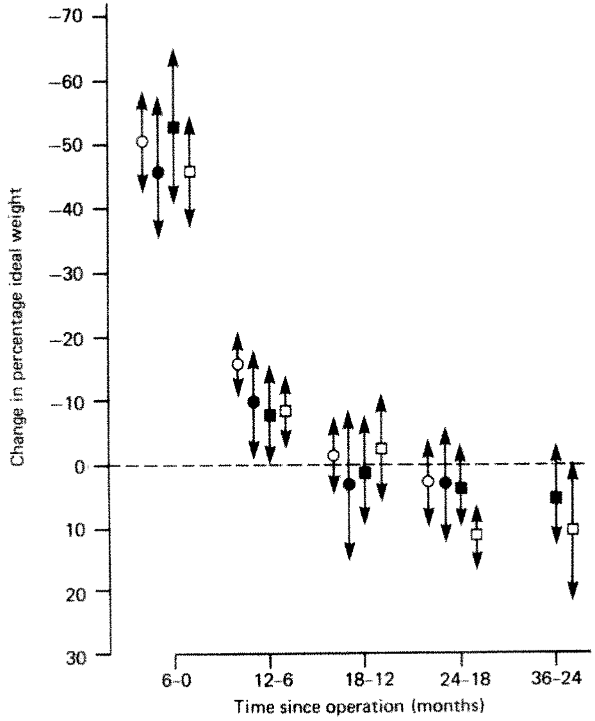

Figure 7 *Comparison of weight loss between patients with the four bands using postoperative change in percentage ideal body-weight at 6-monthly intervals up to 2 years and then at 3 years. The mean and 95 per cent confidence intervals are shown for each group. Zero represents no change in weight, i.e. stabilization of weight loss. All groups stabilize by 18 months. At 2 and 3 years, patients in the 5·5 cm group are regaining weight.* ○, *4·5 cm band;* ●, *4·75 cm band;* ■, *5·0 cm band;* □, *5·5 cm band*

postoperative supervision by a trained dietitian over many months was not fully appreciated.

Therefore we adopted the Mason vertical banded gastroplasty technique[3], with modifications described in detail above, which we believe are necessary for its success. These include accurate measurement of pouch size which is known to be grossly inaccurate if estimated[16,17]. Furthermore size varies with pressure and we have chosen to measure volume at a pressure of 25 cmH_2O.

Double staple line partitioning minimizes the risk of staple line dehiscence[18] and the double cartridge instrument is recommended[19]. Little is known about gastric staple line healing which is thought to take place in 4–6 weeks but may take as long as 3 months. It is important to prescribe liquids only for the first 6 weeks and preferably for 3 months if the patient is compliant and taking in sufficient calories; overfilling with purées and semisolids in the early postoperative weeks may well cause damage and early staple line dehiscence[20], which can be diagnosed only by barium study and endoscopy.

Serosal reinforcement of the circular staple window in the stomach is recommended to minimize leakage (nil in this series), and the integrity of the pouch and staple line should be tested by methylene blue instillation.

The importance of band size measurement is made clear when comparing the failures of 5·5 cm external circumference bands with the success of those of 4·5–5·0 cm. Mason has confirmed that 5·5 cm bands will eventually fail[1,21]. We have reoperated on four patients in this category and have made a new small 15 ml pouch with a 4·75 cm band, and all patients have had long-term success[22,23]. We now fashion a 4·75 cm band as the risk of stenosis is higher when the band is made tighter.

The incidence of stomal stenosis is reported to be in the region of 20 per cent[24]. However as the inability to take solid food often continues for up to 6 months, further investigation is necessary only if this persists longer. Of our five cases of stomal stenosis three have required dilatation: two needed two dilatations and one subsequently needed a pouch-gastrostomy by side-to-side anastomosis which in 2 years was followed by a small weight gain. Two patients who had stenosis did not require dilatation; the reason for this became apparent at endoscopy which showed staple line dehiscence.

The most common complication in hospital is early vomiting caused by a rushed intake; it rapidly resolves if intake is restricted for 24 h. Liquidized or puréed foods after 1–2 months reduce the likelihood of obstruction of the stoma and avoid vomiting and the risk of staple line dehiscence.

Specific food intolerances are common postoperatively especially for red meat, bread and fruit. Constipation is also common and is due to inability to take dietary fibre. The rapid early weight loss is because a very low calorie diet is inflicted on the patient and it is important that the patient does not approach near-starvation calorie levels—hence the need for close supervision by a dietitian to avoid the hazards of excess lean tissue loss and to attain a slow, sustained weight loss over 9–12 months with stabilization thereafter to near-ideal weight levels.

A gastroplasty self-help group has proved invaluable especially for new candidates for operation as well as those under regular postoperative follow-up. It is particularly helpful for spouses and closely related family members to attend. Questions of diet, clothing, daily exercise and social problems of family readjustment are discussed.

We conclude that the surgical treatment of morbid obesity by vertical banded gastroplasty is an effective means of producing successful long-term weight reduction and social rehabilitation. The long-term aim is dietary modification and the operation is the initial treatment, undertaken only after prolonged preoperative assessment. There is no long-term information available on the pouch size after 5–10 years. The very small initial pouch size of 10–20 ml provides a long time lag before any expansion takes place. By that time it is hoped that diet and eating habit modifications should be firmly established.

Acknowledgements

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Cardia carcinoma considered as a distinct clinical entity

B. Husemann

Department of Surgery,
University of Erlangen-Nürnberg,
Postfach 35-60,
8520 Erlangen-Nürnberg, FRG
Correspondence to:
Professor B. Husemann

From 1 January 1969 until 31 December 1985, gastric resections were performed in 937 patients with carcinoma of the stomach and 422 patients with carcinoma of the cardia. During this period, the general frequency of cardia carcinoma increased continuously from 6·6 per cent (1969–71) to 37·5 per cent (1984–85) and a corresponding decrease of carcinomas in other sites was observed. Early carcinomas (pT1) of the oesophageal margin (n = *10, 2·4 per cent) were diagnosed less often than early carcinomas in other sites* (n = *177, 18·9 per cent). Whereas 51·4 per cent of all resected carcinomas of the stomach showed no lymph node metastases (pN0), only 14·1 per cent of cardia carcinomas belonged to this category. With respect to operative treatment, Laurén's classification which defines the required margin of clearance according to diffuse type (frequency in cardia carcinoma 43 per cent, in other stomach sites 51 per cent), is of great significance. We believe that extensive oesophageal resection is necessary for patients with such difficult tumours. The pattern of metastasis in cardia carcinoma is similar to that of cancer in other stomach sites, the preferred area is the regional lymph nodes on the lesser curve (83 per cent). Histological classification and metastasis pattern show that cardia carcinoma is a type of carcinoma of the stomach which must be treated according to the criteria of stomach cancer surgery.*

Keywords: Carcinoma, stomach, cardia, surgery

The name 'cardia' to denote the 'mouth of the stomach' has been attributed to Galen, and malignant tumours of this region are known as cardia carcinomas. The definition is, however, not unequivocal. Operative tactics force surgeons to deal with this tumour as if it were an oesophageal tumour[1,2], whereas from an oncological point of view it can be classified as a stomach carcinoma[3–8]. Using epidemiological and histopathological data collected at the Department of Surgery of the University of Erlangen, we sought to clarify this problem.

Patients and methods

In the present study, a malignant lesion at the oesophageal–gastric margin is classified as a cardia carcinoma when this is a carcinoma of the fundus of the stomach which has reached the cardia or has crossed over to the distal oesophagus[9–11]. By definition the following tumours are not included: carcinoma confined to the fundus of the stomach, extensive carcinoma of the proximal third of the stomach with infiltration of several sections of the stomach, carcinoma in a Barrett's oesophagus[8,12,13] and squamous cell carcinoma of the distal oesophagus.

Adenocarcinoma in a Barrett's oesophagus and squamous cell carcinoma are carcinomas of the oesophagus.

All patients who underwent resection of cardia carcinoma between 1 January 1969 and 31 December 1985 were included in the analysis. Patients with carcinoma of the stomach in other sites during the same period served as controls. Clinical and histopathological data were prospectively recorded. Data from 422 patients with a cardia carcinoma and 937 patients with carcinoma of the stomach in other sites were analysed.

The histopathological assessment of the specimens (fixed in formalin), was done using the following classifications: pTNM, Borrmann's classification[14], histological classification using Laurén's method[15] and the 1977 UICC pathological staging. Laurén's classification was made according to the predominant type. All lymph nodes present in the fixed specimens were classified according to topography and were microscopically examined for malignancy at intervals of 300 μm.

When necessary, statistical significance was determined using a χ^2 test or trend test.

Results

Epidemiological data

The overall rate of cardia carcinoma, compared with that of all carcinomas of the stomach was 31 per cent (422 of 1359). In the first 15 years of the study period, we observed a shift in the pattern of stomach carcinoma towards the cardia (*Table 1*). In 1970, the ratio of cardia carcinoma to stomach carcinoma in other sites was 1:5·6, and by 1980 there was an increase in cardia carcinomas which changed the proportion to 1:1·7. The increase was observed in both sexes.

When one analyses the frequency of male and female patients with respect to tumour localization, one finds differing trends (*Table 2*). The predominance of male patients remains but although the number of female patients remained the same, the male:female ratio of cardia carcinomas increased from 0·27 to 0·53 in the period 1972–85. Because of the small number of patients who underwent resections for cardia carcinoma during the period 1969–71, a male to female comparison was not possible.

Histological classification

Histological classification of the tumours according to the World Health Organization classification showed no fundamental differences between the two sites (*Table 3*). The difference in the frequency of signet-ring cell carcinoma at the cardia (6·4 per cent) and at other sites in the stomach (12·5 per cent) was significant. This observation can be explained by Laurén's classification (*Table 4*): while the frequency of intestinal and diffuse type is nearly the same in carcinoma of the stomach in other sites, the intestinal type is the predominant type at the cardia. When analysing trends over time, we found that the frequency of the diffuse type of cancer at the cardia increased from around 30 per cent to about 50 per cent, while the rate of the diffuse type of carcinoma at other sites in the stomach remained relatively constant during the entire observation period.

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Table 1 *Relative frequency of carcinoma of cardia and of other stomach sites in the period 1969–85*

	Number of patients		Cardia cancer as percentage of all stomach cancer		
Time interval	Cardia cancer	Stomach carcinoma in other sites	Male (*n* = 901)	Female (*n* = 458)	All patients (*n* = 1359)
1969–71	23	137	13·9	15·4	14·4
1972–74	47	144	29·8	14·9	24·6
1975–77	57	172	29·2	16·0	24·9
1978–80	102	192	22·3	27·8	34·7
1981–83	127	183	43·0	37·3	41·0
1984–85	66	109	36·4	40·4	37·7
Total	422	937	33·4	26·4	31·0

Table 2 *Male:female ratio in cardia carcinoma relative to carcinoma elsewhere in the stomach*

	Male:female ratio	
Time interval	Cardia cancer	Stomach cancer in other sites
1969–71	—	1:0·47
1972–74	1:0·27	1:0·65
1975–77	1:0·27	1:0·58
1978–80	1:0·36	1:0·57
1981–83	1:0·48	1:0·60
1984–85	1:0·53	1:0·40
Total	1:0·40	1:0·56

Table 3 *Histological classification of cardia carcinoma relative to carcinoma at other sites in the stomach*

	Localization of the tumour	
Histological classification (WHO, 1977)	Cardia (*n*=422)	Other stomach sites (*n* = 937)
Adenocarcinoma		
Papillary	24 (5·7)	28 (3·0)
Tubular	253 (60·0)	502 (53·6)
Mucinous	12 (2·8)	23 (2·5)
Signet-ring cell carcinoma	27 (6·4)	117 (12·5)
Adenosquamous carcinoma	4 (0·9)	0
Undifferentiated carcinoma	92 (21·8)	229 (24·4)
Unclassified carcinoma	5 (1·2)	36 (3·8)
Others	5 (1·2)	2 (0·2)

Values in parentheses are percentages. WHO, World Health Organization

Table 4 *Changing pattern of histological type of gastric cancer in the period 1969–85*

	Cardia cancer		Stomach cancer in other sites	
Time interval	Diffuse type	Intestinal type	Diffuse type	Intestinal type
1969–71	6 (35)	11	53 (52)	49
1972–74	9 (24)	28	69 (55)	57
1975–77	12 (26)	34	77 (50)	77
1978–80	48 (51)	46	108 (58)	77
1981–83	53 (49)	56	76 (46)	89
1984–85	31 (48)	33	50 (46)	59
Total	159 (43)	208	433 (51)	408
Unclassified	55/422		96/937	

Values in parentheses are percentages calculated as diffuse type over all tumours

Table 5 *Pattern of macroscopic tumour classification (Borrmann) in cardia carcinoma relative to carcinoma at other gastric sites*

	Localization of the tumour (%)	
Macroscopic tumour type	Cardia (*n* = 422)	Other stomach sites (*n* = 937)
Early gastric carcinoma	2·7	20·8
Borrmann I	11·7	8·2
Borrmann II	22·7	21·8
Borrmann III	36·1	27·3
Borrmann IV	26·8	21·9
Unclassified	2·4	4·0

Table 6 *pTN classification of cardia carcinoma relative to carcinoma elsewhere in the stomach*

	Localization of the tumours (%)	
pTN classification	Cardia (*n* = 422)	Other stomach sites (*n* = 937)
pT1	2·4	18·9
pT2	49·4	43·9
pT3	40·1	30·7
pT4	8·2	6·5
pN0	14·1	51·4
pN1	33·4	17·1
pN2	42·5	24·3
pN3	10·0	7·2
pNx	12·6	17·0
Unclassified	0·7	1·3

The classification of the tumours according to their macroscopic appearance (Borrmann's classification) showed no differences between cardia and other stomach carcinoma (*Table 5*). As Bormann's classification shows, and this is confirmed by the pTNM classification (*Table 6*), cardia carcinomas are more likely to be found at an advanced stage than stomach carcinomas at other sites. Early cardia carcinomas are rare (2·4 per cent) compared with early carcinomas in other areas of the stomach (19·1 per cent). Most cardia tumours were classified in stages pT3 and pT4. Only 14·1 per cent of all resected specimens had no metastases in regional lymph nodes (pN0), compared with 51·4 per cent in other stomach carcinomas. Correspondingly, 86 per cent of all cardia carcinoma resections belonged to stages III and IV, whereas this was the case in only 55 per cent of carcinomas elsewhere in the stomach.

Dissemination of cardia carcinoma

Regional lymph node metastases from cancers of the cardia are found in the same sites as in other stomach carcinomas. The

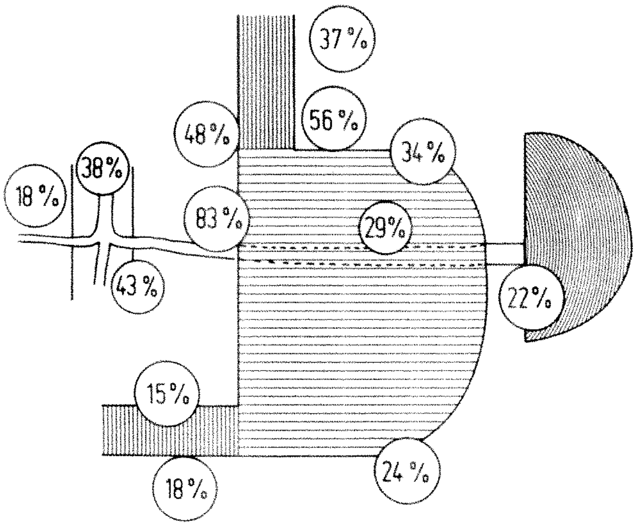

Figure 1 *Pattern of lymph node metastasis in 422 patients with cardia cancer*

main drainage takes place over the lesser curvature to nodes along the left gastric artery (83 per cent tumour involvement) to nodes around the coeliac artery (38 per cent tumour involvement). In about one-third of all patients in the present study of cardia carcinomas we found lymph node metastases along the greater curvature as well as along the splenic artery (*Figure 1*). In contrast to stomach carcinoma of the proximal third, in cardia carcinoma the paracardial and paraoesophageal lymph nodes were frequently tumour-infiltrated (48 and 37 per cent respectively). This mediastinal infiltration was of particular significance in planning resection.

Discussion

In the past three decades, the face of stomach carcinoma has changed. Three aspects are particularly striking: 1) the global frequency of carcinoma of the stomach has decreased or remained the same[16-19], while the frequency of tumours at other sites has increased; (2) parallel to this, there is a pylorocardial shift in tumour location[2,4,5,20,21]; and (3) at the same time, the predominance of male patients has diminished.

In our own patients we observed not only a relative increase but an absolute increase from 7 to 40 cases per year in the number of cardia carcinomas diagnosed during the observation period. The total number of resected stomach carcinomas at other sites remained constant at about 60 per cent. The data of Paterson *et al.*[17] in London must be similarly interpreted. The total number of cases during the observation periods 1951–55 and 1981–85 remained the same ($n = 96$ and $n = 94$), but the frequency of tumours in the proximal third of the stomach increased from 17 to 37, while the number of tumours in the middle and lower third of the stomach declined from 79 to 57. Such shifts must, however, be seen in a critical light when the series of patients is not homogeneous and patients are drawn from a large area. Further bias may result from the changing catchment areas of individual clinics and a changing specialization of different surgeons.

The increasing significance of cardia carcinoma is beyond doubt. We increasingly face the decisive question: in performing surgical therapy, should we follow the principles governing oesophageal surgery[1,2,20] or those governing the surgery of carcinoma of the stomach[4-7,15,21,22]?

The answer is extraordinarily difficult, in so far as cardia carcinoma has not been uniformly defined[10,11,23] nor are the described operative techniques identical. The classification into three types by Siewert *et al.*[11] is of theoretical interest. However, with respect to operative therapy, type I should be included among the malignant tumours of the oesophagus. Separating type II and type III can be difficult, but is easy in many tumours. This separation is of minor importance because the treatment for types II and III (Siewert's classification) is, with some limitations, identical to that used for Laurén's histological classification. Taking the classification used in the present paper as a basis, and on the strength of the histological results and pattern of metastasis, we regard cardia carcinoma as more akin to a carcinoma of the stomach which should be treated according to the principles of stomach cancer surgery.

The most important argument against this proposal is the high rate of local recurrences in the area of the oesophagojejunostomy as well as the relatively high rate of infiltration of mediastinal lymph nodes. The need for extensive oesophageal resection is based on these findings, and cardia carcinoma is consequently classified by some as an oesophageal carcinoma[1,2,20]. This results in a tendency to favour conservative techniques such as forms of endoscopic tumour management[24]. In our opinion, this is not justified.

As is the case of other stomach carcinomas, the histological type[3,5,15] should be considered in order to minimize local recurrences when undertaking surgery for cardia carcinoma[13]. Laurén's diffuse type is characterized by discontinuous growth, the appearance of which can mimic that of multiple tumours. A larger margin of clearance is therefore required for this tumour type (10 cm *in situ*) than for the intestinal cell type (4 cm *in situ*). If we consider these required margins of clearance, the apparent discrepancy in our views on cardia carcinoma disappears. A short distal oesophageal resection is sufficient for the intestinal type. In contrast, an extensive oesophageal resection with a high intrathoracic or cervical anastomosis is necessary to cure the diffuse type. If we take into account the frequency of both types, then classifying cardia carcinoma as an oesophageal carcinoma implies over-treatment for more than one-half of patients. Although extensive oesophageal resection is adequate in patients with the diffuse type, because we are dealing with a stomach cancer, substituting the oesophagus by an extended pedicled stomach is inadequate from an oncological point of view. We consider that this tumour type requires extensive oesophageal resection with total gastrectomy.

Hence, cardia carcinoma is an exception among the malignant tumours of the stomach as, in order to achieve a cure, the criteria which apply to treatment of stomach as well as to oesophageal carcinoma need to be taken into account. Cardia carcinoma should be considered a separate entity in order to obtain the best results for the patient. Finally, the use of Laurén's histological classification is essential if we are to avoid over-treatment as well as avoid a margin of clearance that is too narrow.

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Announcement

Association of Surgeons in Training

Membership of the Association is open to all senior registrars holding accredited posts in general surgery, urology, plastic surgery, neurosurgery, orthopaedics, cardiothoracic surgery and paediatric surgery. Registrars in the above specialties who are 2 years post-fellowship may also apply. The Association represents the views of members on all matters relevant to surgical training besides holding scientific and social meetings. If you are not a member please contact the Secretary, Andrew McIrvine, 35, Elsie Road, Dulwich, London SE22 8DX, for details of membership, local representatives and forthcoming meetings. The next AGM will be held in Cardiff from 21–23 September 1989.

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Somatostatin analogue SMS 201-995 (octreotide) as a possible solution to the dumping syndrome after gastrectomy or vagotomy

J. N. Primrose and
D. Johnston

University Department of Surgery,
The General Infirmary, Leeds, UK
Correspondence to:
Mr J. N. Primrose, St. James's
University Hospital, Beckett Street,
Leeds LS9 7TF, UK

The dumping syndrome, which may follow partial gastrectomy or truncal vagotomy and drainage, may be refractory to treatment. The aim of this study was to determine the effect of the somatostatin analogue, SMS 201-995 (octreotide), on dumping provoked by hypertonic glucose. Ten patients with symptoms and signs of dumping were studied. After a dumping provocation test with placebo, all patients developed severe symptoms: seven patients had early dumping, two had both early and late dumping and one had late dumping alone. With either 50 or 100 μg SMS 201-995, the symptoms of early dumping were much reduced in all patients, and those of late dumping were completely abolished. The packed cell volume, pulse and systolic blood pressure changes of early dumping were significantly reduced by SMS 201-995 and the fall in blood glucose in patients with late dumping was abolished. SMS 201-995 may be a useful treatment for early and late dumping.

Keywords: Dumping, gastrectomy, vagotomy and drainage, somatostatin analogue SMS 201-995

The dumping syndrome, first described by Mix in 1922[1], is a symptom complex consisting of light-headedness, dizziness, fainting, nausea, abdominal distension and discomfort, with or without diarrhoea, which follows various forms of gastric surgery, particularly truncal vagotomy and drainage and partial gastrectomy. These symptoms are typically provoked by eating and appear to be related to the destruction of some of the normal regulatory functions of the upper gastrointestinal tract: rapid gastric emptying[2] is certainly important, but the various effects of extragastric vagotomy may also play a part[3]. Dumping is usually divided into two conditions: early dumping, in which fluid is thought to pass from the circulation into the gastrointestinal tract, and late dumping, which is reactive hypoglycaemia. In practice it can be difficult to distinguish clinically between the two and, indeed, many patients suffer from both.

Significant dumping afflicts approximately 5–10 per cent of patients after truncal vagotomy and drainage[4–6] and a similar proportion after partial gastrectomy[4]. Although these troublesome symptoms can often be managed medically by alterations in the diet and way of life or, as in Mix's original paper, surgically[1], a few patients remain refractory to treatment. Most surgeons with an interest in gastroenterology have a number of such 'gastric cripples' attending their clinics and therefore an effective treatment for this condition would be invaluable.

It is known that the plasma concentrations of several gut regulatory peptides are elevated in patients with the dumping syndrome[7–10], although it is not known whether this is a primary or a secondary phenomenon. These findings have, however, stimulated some interest in the use of somatostatin in this syndrome. Somatostatin is a naturally occurring 14-amino-acid peptide hormone which is widely distributed in the gastrointestinal tract. It inhibits the secretion of most gut regulatory peptides, decreases intestinal motility and secretion and reduces the splanchnic blood flow[11]. Two clinical trials on patients with the dumping syndrome, using natural somatostatin, have yielded encouraging results[12,13]. However the clinical use of natural somatostatin is limited since plasma somatostatin is rapidly cleared by circulating peptidases and its half-life in plasma is less than 3 min[11].

SMS 201-995 (octreotide, Sandoz Products Ltd., UK) is a synthetic somatostatin analogue. This octapeptide[14] has been shown to have a plasma half-life of 90 min in healthy volunteers[15]. It has a prolonged duration of action because of its resistance to biodegradation[15] and its high affinity with somatostatin receptors[16]. Oral administration is possible[17] and an oral preparation is currently being formulated. Thus, SMS 201-995 might fulfil many of the requirements of a practical treatment for the dumping syndrome.

The aim of this study was to determine the effect of SMS 201-995 on early or late dumping provoked by a dumping provocation test.

Patients and methods

Ten patients, 7 men and 3 women, with a mean age of 54 years (range 28–75 years), were studied. All patients had undergone some form of gastric surgery in the past and some had undergone multiple operations. The operations that had been performed before the study were Pólya gastrectomy (three patients), antrectomy with Roux-en-Y reconstruction (three patients), antrectomy with jejunal interposition (one patient), truncal vagotomy and gastroenterostomy (one patient), truncal vagotomy and pyloroplasty (one patient); one patient had a selective vagotomy alone, the previously performed gastroenterostomy having been taken down. In three patients (jejunal interposition, Roux-en-Y reconstruction and taking down of gastroenterostomy) the last operation had been performed for symptoms which included dumping. At the time of the study all ten patients had intractable symptoms of dumping which had proved refractory both to dietary manipulations and, in three patients, to revisional surgery.

After an overnight fast, a dumping provocation test was performed on each patient on three occasions using 350 ml 25 per cent glucose solution by the method previously described[18]. Two 5 ml samples of venous blood, 15 min apart, were taken before the test to establish the basal levels of the packed cell volume (PCV) and blood glucose. Samples were taken 10, 20, 30, 45, 60, 90 and 120 min after ingestion of hypertonic glucose for the same estimations. Samples were taken without the use of a tourniquet. The PCV was determined by the use of standard haematological techniques (Coulter counter, Coulter Electronics, Luton, UK) and the blood glucose by the glucose oxidase method.

Sixty minutes before the tests the patient received either a placebo or a subcutaneous injection of 50 or 100 μg SMS 201-995. The pretreatment was given in random order on separate days, so that after the three test days the patient had recevied each of the pretreatments. On each occasion the patient's symptoms, pulse and blood pressure were recorded at the above time points by an observer who was unaware of the treatment given. Unfortunately, owing to failure of venous access, the PCV data were not recorded on one patient after the 50 μg dose of SMS 201-995. In another patient the recording of the PCV, pulse and blood pressure was abandoned after a similar problem following the administration of 100 μg SMS 201-995.

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Table 1 *The symptoms experienced during a dumping provocation test after a placebo and after 50 and 100 μg SMS 201-995 in the ten patients studied*

Patient	After placebo	After 50 μg SMS 201-995	After 100 μg SMS 201-995
1	Dizziness Nausea Diarrhoea	Nil	Nil
2	Fainting Nausea Severe diarrhoea	Mild discomfort Mild diarrhoea	Mild discomfort Mild diarrhoea
3	Dizziness Discomfort Diarrhoea	Nil	Nil
4	Fainting Diarrhoea	Nil	Nil
5	Nausea Dizziness Discomfort	Vague dizziness	Fatigue
6	Sweating Drowsiness	Mild drowsiness	Mild drowsiness
7	Discomfort Dizziness Diarrhoea	Nausea	Nausea
8	Dizziness Headache Discomfort	Nil	Nil
9	Nausea Abdominal pain Diarrhoea	Cold	Cold
10	Fainting Abdominal pain Diarrhoea	Nil	Nil

Statistical analysis was carried out using the Wilcoxon signed rank test.

Informed consent was obtained in all patients before performance of these studies.

Results

When the dumping provocation test was carried out with placebo, all patients experienced severe symptoms. The three most troublesome symptoms described by the patients are shown in *Table 1*, in the order in which the patients reported having experienced them. On the basis of the symptoms and the changes in PCV and blood glucose during the test, it was determined that seven patients had early dumping alone, two had a combination of early and late dumping and one had late dumping alone.

The symptoms of dumping were markedly reduced by both 50 and 100 μg SMS 201-995 (*Table 1*), only one patient having significant residual symptoms. Even in this patient the symptoms were ameliorated. The PCV and blood glucose results from the dumping provocation tests are illustrated in two typical patients: one with early dumping alone (*Figure 1*) and one with late dumping alone (*Figure 2*). The marked increase in PCV, which is the feature of early dumping illustrated in *Figure 1*, was diminished with either dose of SMS 201-995. The glucose tolerance was also reduced in this patient. Symptoms were also completely abolished with both doses of SMS 201-995. In the patient with late dumping (*Figure 2*), no increase in PCV followed the test, but 90 min after ingesting hypertonic glucose, the patient became hypoglycaemic and experienced typical symptoms of late dumping. The hypoglycaemia was abolished by either dose of SMS 201-995, as were the symptoms.

Analysis was carried out on the changes in PCV, blood pressure and pulse in the patients with early dumping. For comparison, the largest increment from the baseline levels in the direction that is commonly observed in early dumping was used for statistical analysis. Thus, for the PCV and pulse rate the maximum rise over baseline was chosen, whereas for systolic blood pressure, the maximum fall was used. The results are shown in *Figures 3, 4* and *5* respectively.

The median rise in PCV in the patients with early dumping (*Figure 3*) was 4·5 per cent with placebo, 1·2 per cent after 50 μg

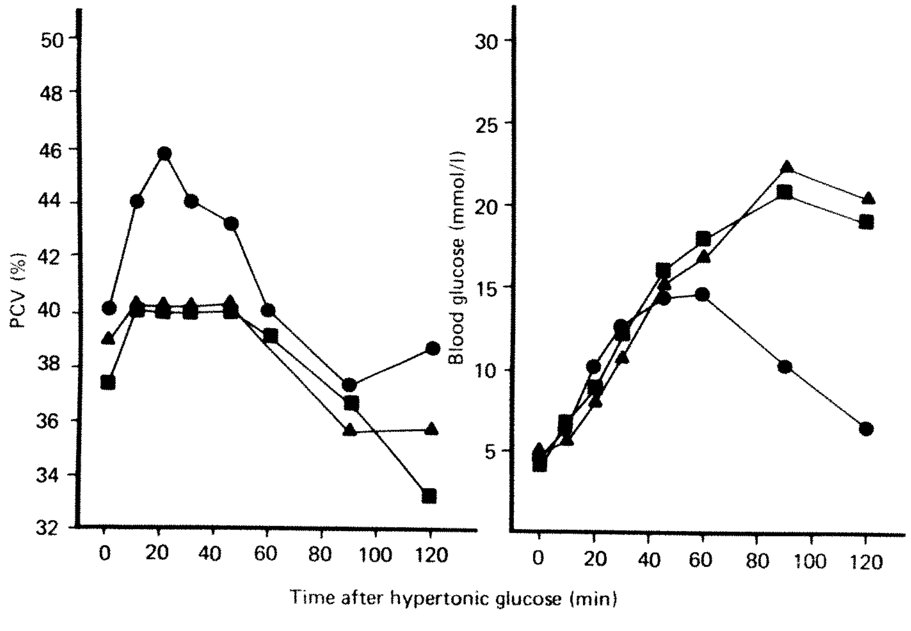

Figure 1 *The packed cell volume (PCV) and blood glucose response to a dumping provocation test in a patient with early dumping after placebo (●) and after treatment with 50 μg (■) and 100 μg (▲) SMS 201-995*

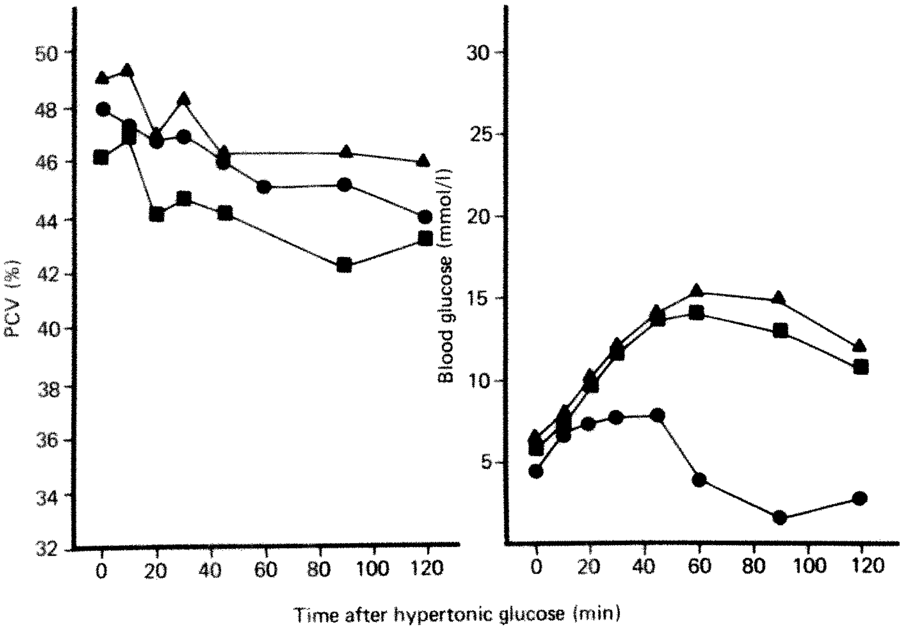

Figure 2 *The packed cell volume (PCV) and blood glucose response to a dumping provocation test in a patient with late dumping after placebo (●) and after treatment with 50 µg (■) and 100 µg (▲) SMS 201-995*

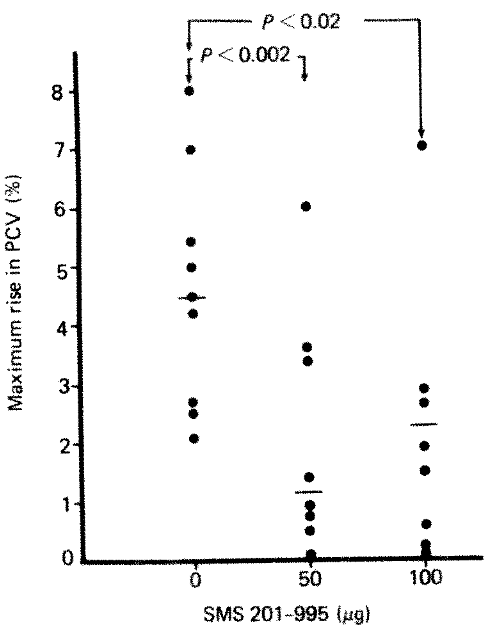

Figure 3 *The maximum rise in packed cell volume (PCV) in nine patients with early dumping after a dumping provocation test with placebo and after 50 µg and 100 µg SMS 201-995*

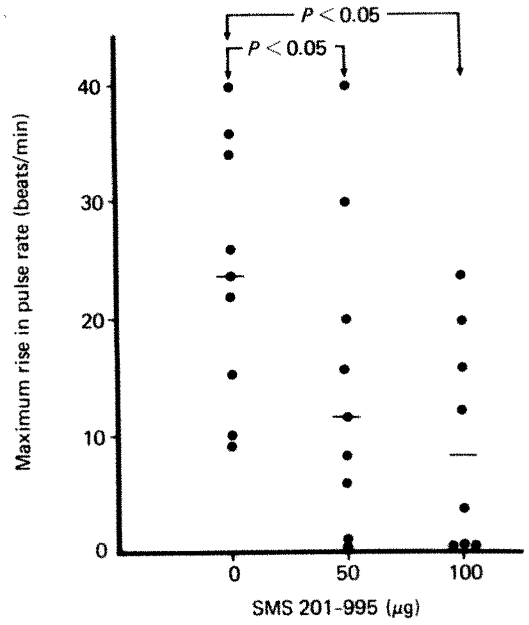

Figure 4 *The maximum rise in the pulse rate in nine patients with early dumping after a dumping provocation test with placebo and after 50 µg and 100 µg SMS 201-995*

SMS 201-995 ($P < 0.002$) and 2·1 per cent after 100 µg SMS 201-995 ($P < 0.02$). Similarly, the median rise in pulse rate (*Figure 4*) was 23 beats/min on placebo, 12 beats/min after 50 µg SMS 201-995 ($P < 0.05$) and 8 beats/min after 100 µg SMS 201-995 ($P < 0.05$). The fall in systolic blood pressure which was provoked when the placebo was given (*Figure 5*) was also significantly reduced by both doses of SMS 201-995 ($P < 0.05$). The fall in the blood glucose concentration which occurred in three patients with late dumping is shown in *Figure 6*. With either dose of SMS 201-995 the hypoglycaemia was abolished in each patient and symptoms of late dumping were absent.

Discussion

Dumping is a troublesome condition which is difficult to treat, and thus its occurrence is best prevented by avoiding truncal vagotomy and drainage or partial gastrectomy wherever possible. This is feasible in the surgical treatment of duodenal and gastric ulceration by the use of highly selective vagotomy, after which the incidence of dumping is very low[5]. However, there are occasions when this form of surgical treatment is inappropriate and because of this, and also because many patients have in the past been treated by means of these more destructive operations, an effective treatment for dumping would be of considerable importance.

We have demonstrated that SMS 201-995 is effective in the treatment of dumping provoked by hypertonic glucose. The symptoms of early dumping were virtually eliminated in nine of the ten patients and the accompanying changes in PCV, pulse and systolic blood pressure were also diminished. In three patients with late dumping the symptoms were completely abolished, as was hypoglycaemia.

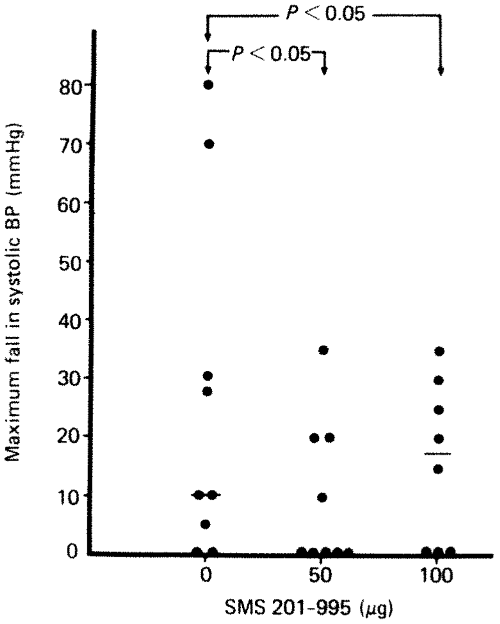

Figure 5 *The maximum fall in systolic blood pressure in nine patients with early dumping after a dumping provocation test with placebo and after 50 μg and 100 μg SMS 201-995*

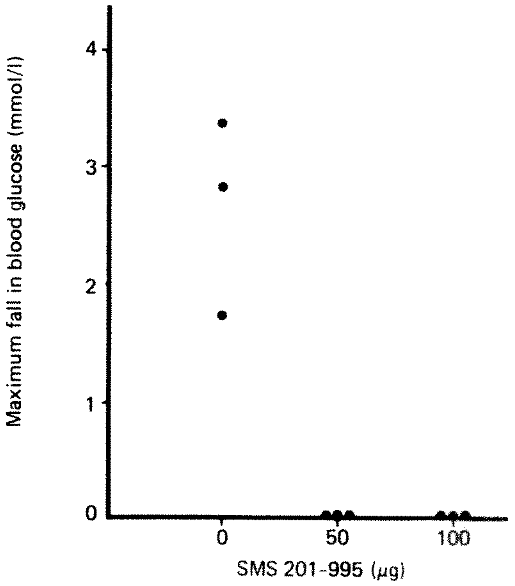

Figure 6 *The maximum fall in blood glucose in three patients with late dumping after a dumping provocation test with placebo and after 50 μg and 100 μg SMS 201-995*

These results are consistent with those of Long *et al.*[12], who studied the effect of natural somatostatin on dumping provoked by hypertonic glucose. They reported similar effects on the PCV and pulse rate with considerable symptomatic benefit to the patient. Reasbeck and Van Rij[13] reported similar results on PCV and pulse, also using natural somatostatin, but failed to demonstrate symptomatic benefit to the patient. This was because the symptoms of dumping were replaced by symptoms of abdominal colic. This effect was not seen in this study, using SMS 201-995.

The mechanism by which SMS 201-995 acts on dumping is not clear. In early dumping it may be that the slowing of gastric emptying which has been demonstrated in patients with dumping after treatment with SMS 201-995[19] may be important. Also, delayed intestinal transit and the reduction in gastrointestinal secretion, which is well documented with regard to somatostatin, may also be important[11]. Dumping is rare after highly selective vagotomy[5] but, when it occurs, is thought to be due to failure of receptive relaxation of the stomach. We have not had the opportunity to study such a patient after highly selective vagotomy and therefore do not know whether SMS 201-995 would be useful in these circumstances. The mechanism by which SMS 201-995 works in late dumping is easier to understand, as reactive hypoglycaemia, which is related to insulin secretion, may be diminished by SMS 201-995. It was noticeable in this study that the 100 μg dose produced no significant benefit over the 50 μg dose and it is possible that smaller doses of SMS 201-995 may be effective in dumping. In addition, the timing of the dose in our study (1 h before the test) means that the compound has a sufficiently long duration of action to be of practical use for a patient who complains of dumping.

The results of this preliminary study suggest that treatment with SMS 201-995 may be valuable in preventing dumping. However, whether the clinical benefit produced in the artificial circumstances of a dumping provocation test can be reproduced in more normal conditions, with the patient eating meals, remains to be seen. In addition, it may be that not all the symptoms associated with dumping may be similarly affected. The pathogenesis of diarrhoea, for instance, may be different from that of dumping[3] and diarrhoea may not respond to revisional surgery, even when this helps the other symptoms of dumping. In this study it was noticeable that diarrhoea was one of the symptoms which was not completely abolished by SMS 201-995, and the mild malabsorption which may occur with SMS 201-995[11] might even contribute to loose bowel actions.

Because the preparation is only available in a form suitable for parenteral administration, clinical trials will have to be confined to patients with the most severe, intractable symptoms. More widespread assessment should be possible when an oral formulation[17] becomes available, and this is expected soon. However, even if a beneficial effect can be demonstrated in patients suffering from dumping, the long-term nutritional and metabolic effects of SMS 201-995 will require careful study. This is particularly important because many patients who have had multiple gastric operations already have nutritional problems.

Acknowledgements

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Delayed return of gastric emptying after gastroenterostomy

S. D. S. Woods and G. J. Mitchell

Department of Surgery, Aberdeen University, Aberdeen, UK
Correspondence to:
Mr S. Woods, PO Box 327,
Caulfield East, 3145 Victoria,
Australia

A retrospective study of patients having gastroenterostomies was undertaken to identify predictive factors for the development of postoperative delayed return of gastric emptying (DRGE). A total of 322 consecutive patients underwent 324 gastroenterostomies; 35 experienced delayed return of gastric emptying. Regression analysis demonstrated preoperative obstruction to be the most significant factor ($P<0.001$)*. Vagotomy was not an independent variable. Age, sex, size of stoma, anastomotic technique, albumin and experience of the operator were not significant factors. Gastroenterostomy in the presence of 'gastric atony' was likely to produce DRGE. In all, 86 per cent of cases resolved spontaneously. Only one case of DRGE was found to have a mechanical cause. Most patients were supported by parenteral nutrition but, with a knowledge of the identified risk factors, more thought could be given to establishing a route for jejunal feeding at the time of surgery.*

Keywords: Gastroenterostomy, ulcer, vagotomy, pancreatic neoplasm

Delayed return of gastric emptying (DRGE) following gastroenterostomy is a problem known to most surgeons and has been referenced in the literature for over 50 years. Lewisohn[1] noted in 1936 that gastric atony was common in long-standing gastric outlet obstruction and could persist after gastroenterostomy. Jones and Eaton[2] postulated in 1933 that 'nutritional oedema' was the cause and suggested a preliminary feeding jejunostomy in the management of such patients.

Dragstedt and Woodward[3] found that vagotomy alone for uncomplicated duodenal ulcer sometimes resulted in DRGE: 15 of 234 patients in his original series required gastroenterostomy for relief of this problem. Subsequently, it has become routine to add a drainage procedure to a vagotomy. Vagotomy and drainage also came to be employed for patients with gastric outlet obstruction. Gastroenterostomy alone ceased to be a common procedure for ulcer disease. Although DRGE continued to be observed, the focus of attention was now on vagotomy as the cause. Experimental work by Nelson *et al.*[4] demonstrated the complexity of the effects of vagotomy on gastric motility. Weinstein *et al.*[5] reported a 17 per cent incidence of DRGE after vagotomy and gastroenterostomy for duodenal ulcer in a series of 73 patients. Although this series included 33 patients with preoperative gastric outlet obstruction, no indication was given that this increased the likelihood of DRGE.

Others[6–9], however, reported that preoperative obstruction increased the incidence of the problem significantly. This led to the conclusion that antecedent gastric outlet obstruction represented a contraindication to vagotomy and gastroenterostomy and that partial gastrectomy was preferable[5,6,7,9–11]. This view has not been universally accepted, given the additional mortality from gastric resection and the knowledge that DRGE will almost always resolve with time[7,9,12].

The aim of this study was to define the incidence of DRGE after gastroenterostomy performed for a variety of conditions. It was hoped thereby to identify patient groups most at risk of developing this complication with a view to minimizing the attendant morbidity.

Patients and methods

The records of all patients recorded as having a gastroenterostomy performed at Aberdeen Royal Infirmary in the 10 years from 1977 to 1986 were examined. The indication for operation, preoperative investigations, operative findings, operative procedure and postoperative course were recorded. A total of 344 patients were identified; four case histories were unobtainable and in 18 documentation was incomplete. This left 322 patients who had 324 gastroenterostomies. There were 196 men and 126 women (M:F ratio, 3:2). Ages ranged from 17–90 years (mean 59 years). Indications for operation were as follows: duodenal ulcer (233), carcinoma of pancreas (40), carcinoma of stomach (30), duodenal and periduodenal malignancy (9); and DRGE after previous surgery (12).

Definitions

The following definitions were used.

Gastric outlet obstruction. This was said to be present preoperatively when the symptoms and signs were suggestive and barium meal, endoscopy, operative findings or a combination of these also supported the diagnosis.

Prophylactic gastroenterostomy. This was performed where no evidence of obstruction existed.

Time at which gastric emptying was established. This was defined as the first day when all of the following criteria were met: patient tolerated oral fluids, no nasogastric tube *in situ*, intravenous fluid therapy discontinued; and no vomiting.

Delayed return of gastric emptying. This was defined as failure to establish gastric emptying by day 8 (see Discussion).

Exclusions

Patients who had previous or concurrent gastric resections were excluded as were those who had operations for morbid obesity.

Analytical method

The following factors were analysed to determine whether they were significant predictors of DRGE: preoperative obstruction, malignancy *versus* benign disease, vagotomy, age, site of gastroenterostomy, technique of gastroenterostomy, and preoperative albumin level.

Analysis was performed using the multiple regression programme in Statworks® (Cricket Software, Philadelphia, Pennsylvania, USA) run on an Apple® (Macintosh, Cupertino, California, USA) personal computer. The effect of gastric atony was analysed using χ^2 with Yates' correction.

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Results

Eighteen patients (5·6 per cent) died within 30 days of operation. Nine patients died within 8 days without establishing gastric emptying; these patients are therefore excluded from further analysis. Six patients established gastric emptying but died within 30 days and are therefore included in subsequent analysis. Three patients died between day 8 and day 30 without establishing gastric emptying. These patients are therefore included in subsequent analysis. Two patients died after 30 days, without having established gastric emptying. These are included in subsequent analysis, but excluded from the above mortality figure.

The deaths were distributed as follows: carcinoma of pancreas (nine), carcinoma of stomach (four), bleeding duodenal ulcer (two), obstructed duodenal ulcer (two), perforated duodenal ulcer (one).

No patient was found, clinically, radiologically or at post mortem, to have an anastomotic leak.

Six patients had another operation before gastric emptying was established: one for bleeding on day 9; one for small bowel obstruction on day 10; four for DRGE on days 10, 17, 19, and 154. The patient with the small bowel obstruction was the only case found to have the mechanical cause for DRGE. These six patients are included in subsequent analysis.

In 76 per cent of cases the site of the stoma was described as posterior, in 12 per cent as anterior and in 12 per cent the site was not stated. All but two gastroenterostomies were performed with a two-layer hand sewn technique. A total of 304 patients with 304 gastroenterostomies established gastric emptying. Gastric emptying was established between day 1 and day 63 (mean, 5·4 days). All patients are considered together in *Table 1*.

All operations except those on patients dying within 8 days without having established gastric emptying, were then sorted into groups on the basis of the indication for operation, and further subdivided into those with preoperative obstruction (*Table 2*) and those without (*Table 3*).

Table 1 *Percentage of patients who established gastric emptying each postoperative week*

Postoperative week when fluids first tolerated	1	2	3	4	5+
Number of patients	270	22	2	7	3
Percentage of total	89	7	1	2	1

Another group of 12 operations could not readily be assigned to either of these categories as some degree of gastric atony was assumed to be present preoperatively. These patients could be considered as having DRGE or at least suboptimal gastric emptying as the indication for their gastroenterostomy. All 12 had previously undergone gastric surgery, eight within the previous month (four, vagotomy and pyloroplasty, one vagotomy and gastroenterostomy and three patching of perforated duodenal ulcer). All eight patients developed DRGE after the second operation.

A total of 37 gastroenterostomies in 35 patients was associated with DRGE; 22 out of 142 (15·5 per cent) were in the obstructed group, seven out of 161 (4·3 per cent) occurred in the non-obstructed group; eight out of 12 (67 per cent) occurred in the gastric atony group.

Of the 37 cases of DRGE 31 (84 per cent) were successfully treated conservatively. Reoperation was performed in six (see above).

Sixteen patients with DRGE were maintained on parenteral nutrition for a total of 28 patient days. One patient had a feeding jejunostomy at his third laparotomy. Four patients developed severe hypoalbuminaemia (serum albumin < 25 g/l). No patient had significant preoperative hypoalbuminaemia.

Analysis

Analysis of possible predictive factors revealed:

(1) preoperative obstruction increased the incidence of DRGE by a factor of 3·6:1 and this was significant ($t=3{\cdot}531$, $P<0{\cdot}001$)
(2) atony due to gastric surgery in the previous month resulted in DRGE in all eight cases compared with 9 per cent in the remainder of the patients combined ($\chi^2=52{\cdot}5$, $P<0{\cdot}001$)
(3) there was insufficient variation in anastomotic technique for meaningful analysis
(4) none of the patients had a low preoperative albumin, rendering analysis of this variable impossible
(5) none of the other factors analysed (vagotomy, age, malignancy, site of gastroenterostomy) achieved significance as an independent variable.

The results of the regression analysis are summarized in *Table 4*.

Table 2 *Incidence of delayed return of gastric emptying in subgroups of patients presenting with preoperative gastric outlet obstruction*

Indication	No. of patients	First day of function Mean	Median	Mode	No. of patients with delay	Delay (%)
Obstructed ulcer	77	5·1	3	4	8	10
Obstructed carcinoma of the stomach	28	4·8	4	3	3	10
Malignant obstruction of the duodenum	9	9·9	6	—	2	22
Obstructed carcinoma of the pancreas	20	8·4	6	—	5	25
Perforated obstructed ulcer	8	14·7	—	—	4	50
Total	142	6·3	4	4	22	15·5

Table 3 *Incidence of delayed return of gastric emptying in subgroups of patients presenting without preoperative gastric outlet obstruction*

Indication	No. of patients	First day of function Mean	Median	Mode	No. of patients with delay	Delay (%)
Perforated ulcer	40	4·3	4	4	0	0
Uncomplicated ulcer	98	4	3	3	4	4
Prophylactic (carcinoma of the pancreas)	16	5·7	6	6	2	12·5
Bleeding ulcer	7	6·7	3	3	1	14·3
Total	161	4·5	4	3	7	4·3

Table 4 *Summary of regression analysis of possible predictors of delayed return of gastric emptying*

Variable name	Coefficient	Standard error estimate	*t* statistic	Probability > *t*
Obstruction	0·126	0·036	3·531	0·000
Vagotomy	0·046	0·074	0·623	0·534
Posterior stoma	−0·044	0·058	−0·756	0·450
Malignancy	0·068	0·075	0·912	0·362
Age	0·000	0·001	0·350	0·727

Discussion

We have chosen in this paper to discuss the time at which gastric emptying was established. One cannot imply that this necessarily coincides with functioning of the gastroenterostomy. Where preoperative obstruction existed, this could be inferred, but it may be in the 'prophylactic' group that emptying recommenced via the pylorus in some patients. None the less, this made no practical difference to the identification of predictors of DRGE, or to the management of these patients.

The published incidence of DRGE after gastroenterostomy varies considerably, with rates from 0·5 to 27 per cent reported[5,7,9,13-15]. Most series have concentrated on duodenal ulcer surgery[5,7-9,13], but the problem has also been noted in patients with carcinoma of the pancreas[14,15]. Less seems to be known about the incidence when the gastroenterostomy has been performed for other indications. Some of the variation may be due to different criteria for defining 'delay'; 8[16], 10[7,9] and 14[8] days have all been used. A mathematical model based on the mean plus three standard deviations has been employed[9]. This does not seem appropriate in the heterogeneous group such as our series in which a normal distribution could not be anticipated. We chose 8 days as this was the time that most clinicians began to investigate the problem and initiate nutritional support. It is perhaps somewhat arbitrary, but there would have been little difference in our figures had we chosen 10 days. The overall number of DRGE cases would have been reduced by five. Repeating the regression analysis using 10 days produced a similar level of significance ($P<0{\cdot}001$).

Our results demonstrate that the only significant predictors are obstruction, or gastric atony following recent surgery. Although old age, malignancy and anterior stomas were all associated with an increase in the incidence of DRGE, analysis revealed that they were not significant independent variables. The possibility of a type 2 error should not be discounted, however. Malignancy, in particular, came close to achieving significance. There is a close correlation between increasing age and malignancy. When age is removed from the regression equation, malignancy achieves significance. We suspect that larger numbers would confirm this to be an independent variable. Vagotomy was associated with a lower incidence, but again was not a significant independent variable. It seems, therefore, that vagotomy *per se* cannot be blamed for this phenomenon in the majority of cases. Terms such as 'post-vagotomy gastric atony' may be misleading.

Hypoalbuminaemia has long been implicated as an aetiological factor. Although four patients developed severe postoperative hypoalbuminaemia, none had evidence of this preoperatively and it is therefore of no use as a predictor. None the less it is possible that in centres where patients present later with advanced malnutrition, this may be an important factor.

No consistent plan for management emerged from this study. Patients invariably underwent contrast examinations which were reported as demonstrating stomal oedema, gastric atony or no abnormality. There were no perceptible differences in the radiographic findings between those patients chosen for reoperation and those treated conservatively. A total of 84 per cent of patients responded successfully to conservative treatment and it seems likely that this figure could have been higher had more patience been forthcoming with four of the remaining patients. Given the likelihood of spontaneous resolution and the disappointing results of early reoperation, there seems to be little indication for early intervention in the majority. A contrast study can still be justified, however, as it may exclude a mechanical problem such as small bowel obstruction or intussusception of the stoma.

Metoclopramide was tried on some patients, but in such a haphazard manner that no conclusions could be drawn regarding its efficacy. McLelland and Horton[16] reported a 100 per cent success rate in a group of patients with DRGE after vagotomy and pyloroplasty. In contrast, Sheiner and Catchpole[17] reported no success at all with metoclopramide alone, but encouraging results with the addition of bethanechol in a small group of patients.

The main task of the clinician in managing this problem is providing adequate nutrition. Here this was achieved with parenteral nutrition, but this has actually been shown to reduce gastric emptying[18]. Furthermore it is expensive and entails the risks of central venous cannulation.

Since 1902[19] jejunostomy has been advocated as an adjunct to gastric surgery. It has been recommended specifically for non-functioning gastroenterostomy[20]. With the availability of fine-bore nasoenteric tubes and needle jejunostomy kits, it is worthwhile considering the prophylactic establishment of a jejunal feeding route in high-risk patients. If this is not undertaken at the time of surgery, a tube can still be introduced endoscopically once DRGE has been diagnosed.

We have confirmed that gastroenterostomy is safe and that the problem of DRGE almost invariably resolves with time. Better awareness of the predisposing factors and the natural history of this condition should lead to improved management. We can see no justification for favouring gastrectomy for obstructed ulcers on the evidence presented here.

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Case report

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Intussusception presenting as ileal reservoir ischaemia following restorative proctocolectomy

W. A. Kmiot and M. R. B. Keighley

The General Hospital, Steelhouse Lane, Birmingham
B4 6NH, UK
Correspondence to: Mr W. A. Kmiot

Intussusception is a rare cause of intestinal obstruction in adults[1]; it can be treated in the early stages by hydrostatic reduction[2]. We report the first case of ileal afferent limb–ileal reservoir intussusception following restorative proctocolectomy.

Case report

A 21-year-old Greek man, with a 10-year history of ulcerative colitis, was referred for surgery. After total colectomy and rectal excision, an ileal J pouch was constructed and anastomosed to the dentate line using a circular stapling device. No covering ileostomy was used and no mesenteric vascular division was necessary to achieve a tension free ileoanal anastomosis. Histology of the resected specimen showed extensive colitis with no evidence of Crohn's disease or carcinoma. On the fourth postoperative day, the patient complained of sudden-onset, constant lower abdominal pain which, over the next 48 h, became increasingly severe. It was associated with a tachycardia of 140 beats/min, a temperature of 39·5°C and lower abdominal tenderness. A contrast enema showed the staple lines to be intact, but the afferent ileal limb looked rigid with an effaced mucosa. The actual pouch contained filling defects suggestive of intussusception (*Figure 1*). At laparotomy, the pouch was oedematous and mottled from ischaemia, but was not gangrenous. An end ileostomy was constructed and the pouch excised.

Histology showed the distal pouch close to the initial anastomotic staple line to be microscopically normal. The afferent ileal limb showed localized haemorrhagic infarction with ischaemic necrosis extending to the upper, adjacent area of the pouch. There was submucosal venous thrombosis in the upper pouch but the major mesenteric arteries and veins were normal. Postoperative progress was stormy initially with the patient requiring intensive care, circulatory support and parenteral nutrition. Subsequently he made an uneventful recovery.

Discussion

The most common complications following restorative proctocolectomy and ileal reservoir formation are small bowel obstruction and pelvic sepsis occurring in 10–20 per cent and 5–20 per cent respectively[3,4]. In these cases surgical intervention is required in 20–40 per cent. Pouch ischaemia in many cases is encountered at operation and various vascular manoeuvres have been described to enable the ileal reservoir to be brought down to the dentate line without traction on the mesentery or undue tension on the pouch–ileal anastomosis[5].

Only 20 per cent of adults with intussusception present in the classical manner with vomiting, episodic abdominal colic, palpable mass and the passage of blood per rectum[1]. Our patient developed the signs and symptoms of intestinal vascular occlusion rather than obstruction.

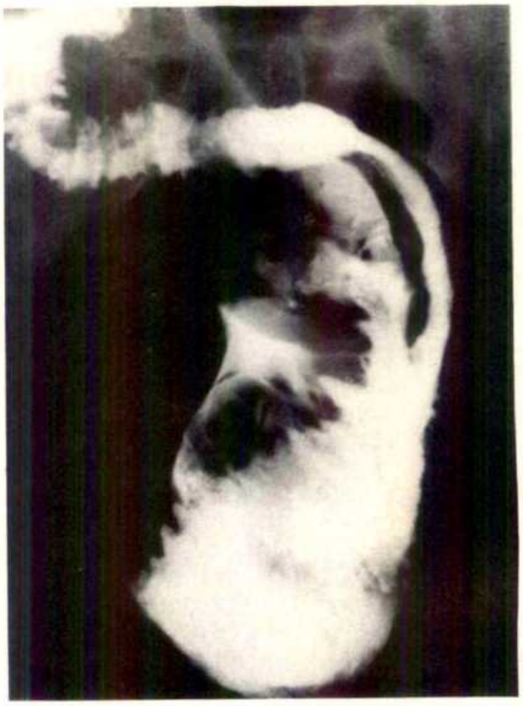

Figure 1 *Contrast enema pouchogram demonstrating filling defects suggestive of intussusception*

The contrast enema was in fact diagnostic, but hydrostatic reduction was unsuccessful. The histological findings of distal pouch viability and localized infarction suggest that afferent ileal limb resection may have been sufficient in this case.

We conclude that ileal afferent limb–ileal pouch intussusception is a cause of postoperative abdominal pain following ileal reservoir formation. Early suspicion will allow an attempt at non-operative hydrostastic reduction. A localized ileal resection may enable the reservoir to be preserved, but use of a proximal ileostomy will probably protect against this rare complication.

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Branched chain amino acids as the protein component of parenteral nutrition in cancer cachexia

D. C. Hunter,
M. Weintraub,
G. L. Blackburn and
B. R. Bistrian

Laboratory of Nutrition and Infection at the Cancer Research Institute, New England Deaconess Hospital, Harvard Medical School, 194 Pilgrim Rd, Boston, Massachusetts 02215, USA

Correspondence to: Dr B. R Bistrian

A prospective randomized trial was conducted to determine the effects of branched chain amino acids (BCAA) as the protein component of total parenteral nutrition (TPN) on protein kinetics in patients with intra-abdominal adenocarcinoma. Nine malnourished patients were given both conventional TPN containing 19 per cent BCAA (AA) and isocaloric, isonitrogenous TPN containing 50 per cent BCAA (BCAA-TPN), in random order. Both [^{13}C]leucine and [^{14}C]tyrosine were employed as tracers to avoid the potential bias due to the different amino acid composition of the two TPN solutions. With BCAA-TPN, leucine and tyrosine flux increased significantly from (mean±s.d.) 158·0±37·2 to 243·5±75·8 $\mu mol\,kg^{-1}\,h^{-1}$ (P<0·025) and from 35·0±8·4 to 42·6±11·0 $\mu mol\,kg^{-1}h^{-1}$ (P<0·05) respectively. Leucine oxidation was significantly higher on BCAA-TPN (24·1±6·3 on AA versus 68·3±37·1 $\mu mol\ kg^{-1}h^{-1}$, P<0·025) while tyrosine oxidation was significantly lower (3·7±1·8 $\mu mol\,kg^{-1}\,h^{-1}$ on AA versus 2·5±2·0 $\mu mol\,kg^{-1}\,h^{-1}$ on BCAA-TPN, P<0·05). Whole body protein synthesis and breakdown was significantly higher on BCAA-TPN by the tyrosine tracer (31·3±7·3 on AA versus 40·1±9·3 $\mu mol\,kg^{-1}\,h^{-1}$, P<0·025 and 33·0±8·4 on AA versus 41·3±11·1 $\mu mol\,kg^{-1}\,h^{-1}$, P<0·05) respectively. Using the leucine tracers both synthesis and breakdown were increased, but not significantly, from 133·8±40·0 to 175·3±65·1 $\mu mol\,kg^{-1}\,h^{-1}$ and from 127·9±33·6 to 167·7±71·2 $\mu mol\,kg^{-1}\,h^{-1}$ respectively. The fractional albumin synthetic rate increased significantly on BCAA-TPN from 4·3±2·9 on AA to 8·0±5·1 per cent per day (P<0·05). The reduction in tyrosine oxidation, suggesting improved protein utilization, coupled with an increase in protein and albumin synthesis, strongly support a positive benefit from BCAA-TPN in cancer cachexia.

Keywords: Cancer cachexia, branched chain amino acids

The cause of cancer cachexia, the progressive weight loss of malignant disease, remains enigmatic. The anorexia of gastro-intestinal malignancy may be related to mechanical obstruction[1] or chronic pain[2], yet the resulting weight loss and biochemical abnormalities often cannot be explained by starvation alone. Weight loss and anorexia may precede other symptoms of malignant disease and not be obviously related to tumour size or the number of metastases[3]. Small lung tumours, unassociated with either pain or gastrointestinal disturbances, can present with profound weight loss. The associated metabolic changes also are not consistent with starvation alone, but are more akin to the metabolic response seen in response to injury[4,5]. The idea that the tumour itself may be responsible for the changes by some intermediary metabolite or hormone has prompted much research without positive identification of a putative agent.

It has been shown in both animals and humans that tumours can be responsible for an increase in whole body protein turnover, reduced protein synthesis in muscle, and an increase in liver protein synthesis[6]. When combined with hypoalbuminaemia and hypotransferrinaemia, these changes are reminiscent of the metabolic response to injury, although of a far lesser magnitude[4,5]. It has also been shown in large tumours that there is an increase in anaerobic metabolism with the production of lactate which is then utilized by the liver via the Cori cycle for gluconeogenesis[7,8]. This process is energetically inefficient and may contribute to the increase in metabolic rate and the disproportionate (over and above starvation alone) weight loss seen with malignant disease or following injury. Branched chain amino acids (BCAA) have been shown to be uniquely effective in reducing protein catabolism in both the injured animal and in humans[9–11]. Recent evidence also supports similar effects of BCAA in cancer-bearing animals and humans[12,13].

As BCAA occupy a unique position in the injury-type metabolism of malignant disease, it was decided to confirm the benefit of infusions of BCAA in a prospective randomized trial in which the patients, acting as their own controls, received both conventional total parenteral nutrition (TPN) and BCAA-enriched TPN (BCAA-TPN). To avoid the potential bias that might result when using an amino acid tracer that is also the major diet variable, both [^{14}C]tyrosine and [^{13}C]leucine were employed.

Patients and methods

Nine malnourished patients with intra-abdominal adenocarcinoma, proved by tissue histology, were chosen for this study.

Signed informed consent was obtained for the study including the use of a radioactive tracer, in full accordance with, and approval of, the Institutional Review Board and Radiation Safety Committee of the New England Deaconess Hospital

All patients underwent a full nutritional history and their height, weight and upper arm anthropometric measurements were made The initial nutritional assessment also recorded the total lymphocyte count and serum secretory protein concentrations, including albumin and transferrin. Patients were tested for delayed hypersensitivity with common recall antigens by the Multitest CMI (Merieux Institute, Miami, Florida, USA). In addition a number of nutritional indices were calculated, including· the basal energy expenditure using the Harris–

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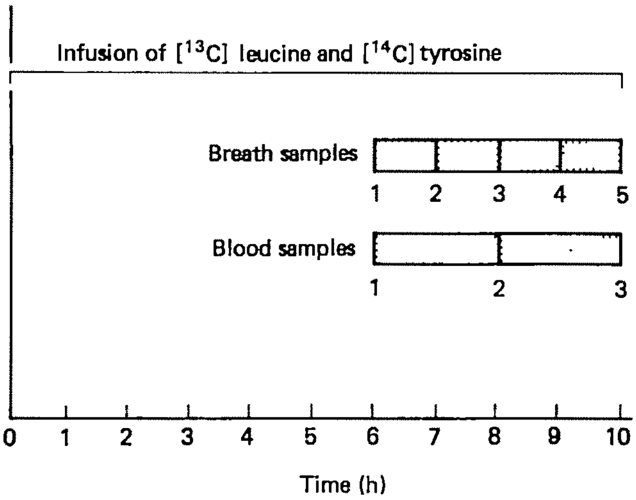

Figure 1 *Experimental design of the infusion study*

Benedict formula[14], hospital prognostic index[15]; catabolic index[16]; creatinine height index[17], and prognostic nutritional index[18].

A 24-h collection of urine for total nitrogen was obtained and the nitrogen balance calculated. (The difference between dietary nitrogen intake and urinary nitrogen excretion plus the faecal and unmeasured nitrogen loss was estimated at 4 g day^{-1})

Patients were studied while receiving a high BCAA formula containing 50 per cent BCAA, or regular TPN containing 19 per cent BCAA (AA) with the order being assigned randomly from a list generated by the pharmacy Patients were then crossed over and studied on the other TPN solution.

The stock solutions from which the TPN was made consisted of Travasol 10 per cent solution (Travenol Laboratories, Deerfield, Illinois, USA) containing 19 per cent BCAA, dextrose 70 per cent and 20 per cent lipid emulsion For the high BCAA solution, Branchamin (Travenol Laboratories) was added to the stock solution in a 4 per cent equimolar solution to bring the BCAA content up to 50 per cent.

The TPN was given as 1 2 g protein kg^{-1} bodyweight day^{-1} and energy as 1 3 × basal energy expenditure day^{-1}by a continuous infusion IMED pump (IMED, San Diego, California, USA) The two study solutions were matched for both nitrogen content and calories. All patients also received their necessary electrolytes, vitamins and minerals Patients received each of the TPN solutions for a minimum of 24 h

Procedure (Figure 1)

The protein turnover study lasted from midnight to 10 00 hours, 50 μCi [^{14}C]tyrosine and 400 mg [^{13}C]leucine having been aseptically added to the TPN solution at the beginning of the period.

During the study, patients were confined to bed and were limited to the consumption of clear fluids. At 06 00 hours and hourly until 10.00 hours, breath samples were collected and analysed for $^{14}CO_2$ and $^{13}CO_2$. At 06 00, 08.00 and 10.00 hours 20 ml whole blood was obtained in heparinized tubes for amino acid analysis. The plasma was separated and stored at −30°C until analysis Baseline enrichments had been obtained before starting the study

At 10.00 hours the flow rate of the IMED pump was measured and the exact volume that was infused was calculated At the same time the patient's oxygen consumption and carbon dioxide production were measured using the Beckman Metabolic Chart (Sensormedics, Anaheim, California, USA).

Analysis and calculations

Plasma amino acid concentrations were measured by ion-exchange chromatography using an amino acid auto-analyser (Dionex D-400, Sunnyvale, California, USA)

$^{14}CO_2$ specific activity was measured on a scintillation counter (Beckman, Fullerton, California, USA) after first trapping 1 mmol CO_2 in a solution of hyamine hydroxide, absolute alcohol and a commercial scintillant (Betafluor National Diagnostic, Somerville, New Jersey, USA) with phenolphthalein as an indicator

$^{13}CO_2$ enrichment was measured by a dual collector isotope ratio mass spectrometer (model 3-60 RMS, Nuclide Corp State College, Pennsylvania, USA).

Plasma [^{14}C]tyrosine specific activity was measured by the method of Garlick and Marshall[19].

[^{13}C]leucine enrichment was determined by isolation of the free amino acid and then derivitization to the N-acetyl, N-propyl ester which was then analysed on the Quadropole Mass Spectrometer (Hewlett-Packard 5985B, Palo Alto, California, USA).

Leucine and tyrosine kinetics, flux, breakdown and protein synthesis were calculated using the Waterlow stochastic model[20] The model explains the following relationship

$$Q=S+O=I+B$$

where Q = flux, S = protein synthesis, O = protein oxidation, I = leucine intake, and B = leucine released by protein breakdown These parameters are expressed as μmol kg^{-1} bodyweight h^{-1}.

Flux is calculated by the equation:

$$Q=\imath\left[\frac{E_\imath}{E_p}-1\right]$$

where $\imath$ is the infusion rate of [^{13}C]leucine, $E_\imath$ is the enrichment of [^{13}C]leucine infused (=atom per cent excess) and E_p is the plasma enrichment of [^{13}C]leucine at plateau. $^{13}CO_2$ (μmol kg^{-1} h^{-1}) production from [^{13}C]leucine oxidation is calculated by the equation

$$V_{^{13}CO_2}=\frac{V_{CO_2}\times E_{^{13}CO_2}}{\text{bodyweight}}\times\frac{60\times 44{\cdot}6}{100\times 0{\cdot}81}$$

where V_{CO_2} is the CO_2 production rate (ml min^{-1}), $E_{^{13}CO_2}$ is the $^{13}CO_2$ enrichment in expired air at isotopic steady state (atom per cent excess) and bodyweight is in kilograms. The constant 60 converts minutes to hours, 44 6 converts millilitres leucine to micromoles leucine (at standard temperature and pressure), 100 changes atom per cent excess to a fraction and 0·81 accounts for $^{13}CO_2$ released by [^{13}C]leucine oxidation but not released from the body bicarbonate pool into the expired air

Leucine oxidation is then calculated as

$$O=V_{CO_2}\left[\frac{1}{E_p}-\frac{1}{E_\imath}\right]\times 100$$

Thus, synthesis can be derived from $S=Q-O$ breakdown by the equation $B_{leu}=Q_{leu}-I_{leu}$ (where I = total leucine infused) and leucine balance = $S-B$.

The above equations are the same for tyrosine except that specific activity is substituted for atom per cent excess, and there is an additional factor in the appearance side of the equation $Q_{tyr}=S_{tyr}+O_{tyr}+N$ (where N = *de novo* synthesis of tyrosine) as tyrosine is a non-essential amino acid. Similarly, isotope balance is estimated as $S-B$, since S is overestimated by the equation $S=Q-O$. To account for this, tyrosine balance was also calculated using results from the leucine studies In this method if one assumes both tyrosine and leucine equilibrate in the same pool, and random breakdown of body protein, then tyrosine and leucine should appear in proportion to their concentration in total body protein (7 5 leucine 3 5 tyrosine)[21]. Thus, if one multiplies the leucine breakdown by 3 5/7·5 one should obtain the amount of tyrosine from protein breakdown (and thus not from synthesis from phenylalanine) (i.e. estimated breakdown of tyrosine = 3 5/7 5 × breakdown of leucine and an estimate for N (*de novo* synthesis): this would be $N=(Q_{tyr}-I_{tyr})-$ estimated B_{tyr})

The albumin was extracted from plasma by precipitation with 20 per cent trichloroacetic acid and then it was resolubilized in an ethanol/water solution. A portion of the extraction was counted while another portion was measured for albumin concentration using a dye-binding technique The specific activity was then calculated on the basis of d p.m. g^{-1} albumin. Statistical analysis included means, standard deviations, paired t tests and linear regression analyses. Protein kinetic data were evaluated using one-tail t tests on the basis that this was a confirmatory trial[13]. Standard two-tailed tests were employed for the plasma amino acid levels The level for significance was set at $P<0\ 05$.

Results

Nine patients, all of whom had demonstrated recent weight loss, completed the study. The mean (±s d.) age was 66·4±6·4 years, the mean weight was 53·8±9·7 kg and mean weight loss was 8 7 kg or 16 per cent of bodyweight. Five of nine patients had suffered a weight loss > 10 per cent of usual bodyweight. Only one patient had a serum albumin concentration >3 g dl^{-1} and the mean concentration was 2·6±0·4 g dl^{-1}. Two-thirds of the patients were anergic to common recall antigens (*Tables 1* and *2*).

The patients remained in a metabolically steady state throughout the study. Their resting energy expenditures, mean 1349 kcal day^{-1} on the BCAA-TPN solution and 1433 kcal

Table 1 *Basic data on the series of nine patients included in the study*

Patient	Diagnosis	Sex	Age (years)	Height (cm)	Weight (kg)	Weight loss (kg)	Albumin (g dl^{-1})
1	Pancreatic cancer	F	63	165	54·5	11·4	3·0
2	Islet cell cancer	F	51	160	53·9	5·1	3·0
3	Gastric cancer	M	65	171	49·9	28·0	2·9
4	Biliary cancer	F	67	155	52·1	2·5	2·1
5	Hepatoma	F	79	104	61·0	1·7	2·3
6	Gastric cancer	M	62	173	62·0	13·0	3·4
7	Biliary cancer	F	63	155	46·4	3·2	2·7
8	Colonic cancer	M	65	187	70·4	7·5	2·3
9	Colonic cancer	F	65	163	34·0	6·0	2·1

Table 2 *Level of transferrin, total lymphocyte count, reaction to an antigen, and nitrogen balance in the nine patients*

Patient	Transferrin* (mg dl^{-1})	Total lymphocyte count† (ml^{-1})	Skin test‡	Nitrogen balance§ (g day^{-1})
1	115	1800	+	−0·4
2	129	640	−	−4
3	150	1350	−	2
4	83	1440	−	−3
5	96	430	−	−4
6	173	2100	+	0
7	170	1460	+	1
8	99	1000	−	0
9	62	1310	−	6

* Normal range, 170–300 mg dl^{-1}; † normal >1500 ml^{-1}, ‡ +, positive reaction to one antigen; −, anergy; § nitrogen balance at start of nutritional support and before test period

Table 3 *Protein kinetics after infusion of leucine and tyrosine*

	Leucine			Tyrosine		
	BCAA	AA	*P**	BCAA	AA	*P**
Flux	243·5±75·8	158·0±37·2	<0·025	42·6±11·0	35·0±8·4	<0·05
Oxidation	68·3±37·1	24·1± 6·3	<0·025	2·5± 2·0	3·7±1·8	<0·05
Breakdown	167·7±71·2	127·9±33·6	n.s.	41·3±11·1	33·0±8·4	<0·05
Synthesis	175·3±65·1	133·8±40·0	n.s.	40·1± 9·3	31·3±7·3	<0·025
Balance ($S-B$)	7·7±44·3	5·9± 8·8	n.s.	−1·2± 2·1	−1·7±1·7	n.s.
Flux oxidized (%)	28·0±12·6	16·5± 7·4	n.s.	5·4± 2·9	10·6±4·7	<0·01
Albumin synthetic rate (% day^{-1})				8·0± 5·1	4·3±2·9	<0·05

Values are mean ±s.d. in μmol kg^{-1} h^{-1} except where shown; * *P* values determined by one-tailed paired *t* test; *S*, protein synthesis minus *B*, protein breakdown; BCAA, 50 per cent branched chain amino acids; AA, 19 per cent branched chain amino acids

day^{-1} on AA, were not statistically different. Their respiratory quotients were 0·90 on BCAA-TPN and 0·92 on AA, demonstrating perhaps slight underfeeding but no significant differences between the diets.

Leucine data were not obtained for three of the patients. Leucine flux and oxidation increased significantly on BCAA-TPN, from 158·0±37·2 on AA to 243·5±75·8 μmol kg^{-1} h^{-1} on BCAA-TPN and from 24·1±6·3 on AA to 68·3±37·1 μmol kg^{-1} h^{-1} on BCAA-TPN respectively ($P<0·025$). Both synthesis and breakdown were increased on BCAA-TPN but not significantly. Synthesis increased from 133·8±40·0 on AA to 175·3±65·1 μmol kg^{-1} h^{-1} on BCAA-TPN and breakdown increased from 127·9±33·6 to 167·7±71·2 μmol kg^{-1} h^{-1}. Isotope balance (synthesis–breakdown) was not significantly different in the two solutions: 7·7±44·3 μmol kg^{-1} h^{-1} on BCAA-TPN and 5·9±8·8 μmol kg^{-1} h^{-1} on AA. The percentage of the flux oxidized was increased on BCAA-TPN but again failed to reach statistical significance (16·5±7·4 per cent on AA and 28·0±12·6 per cent on BCAA-TPN).

This situation was closely simulated using the tyrosine tracer. Tyrosine flux increased from 35·0±8·4 on AA to 42·6±11·0 μmol kg^{-1} h^{-1} on BCAA-TPN ($P<0·05$) and there was significant improvement in protein synthesis from 31·3±7·3 on AA to 40·1±9·3 μmol kg^{-1} h^{-1} on BCAA-TPN ($P<0·025$). Breakdown also increased significantly from 33·3±8·4 on AA to 41·3±11·1 μmol kg^{-1} h^{-1} on BCAA-TPN ($P<0·05$) but the increase in protein synthesis was not as great, so that isotope balance, reflecting protein balance, was improved although not to a level of statistical signficance (from −1·7±1·7 on AA to −1·2±2·1 μmol kg^{-1} h^{-1} on BCAA-TPN). Tyrosine oxidation decreased from 3·7±1·8 μmol kg^{-1} h^{-1} on AA to 2·5±2·0 μmol kg^{-1} h^{-1} on BCAA-TPN ($P<0·05$). The percentage of the flux oxidized was also decreased on BCAA-TPN from 10·6±4·7 per cent on AA to 5·4±2·9 per cent ($P<0·01$). There was a significant increase in albumin fractional synthetic rate from 4·3±2·9 on AA to 8·0±5·1 per cent per day ($P<0·05$) when receiving BCAA-TPN (see *Table 3* for summary).

The results of the patients' amino acid profiles (*Figure 2*) revealed that BCAA-TPN had no effect on the concentrations of taurine, aspartate, glutamine, glutamate and alanine. The levels of threonine (0·158±0·041 on AA and 0·094±0·024 μmol ml^{-1} on BCAA-TPN), serine (0·112±0·030 on AA and 0·087±0·019 μmol ml^{-1} on BCAA-TPN), glycine (0·432±0·102 on AA and 0·324±0·092 μmol ml^{-1} on BCAA-TPN) and methionine (0·062±0·027 on AA and 0·044±0·032 μmol ml^{-1} on BCAA-TPN) were all significantly reduced on BCAA-TPN

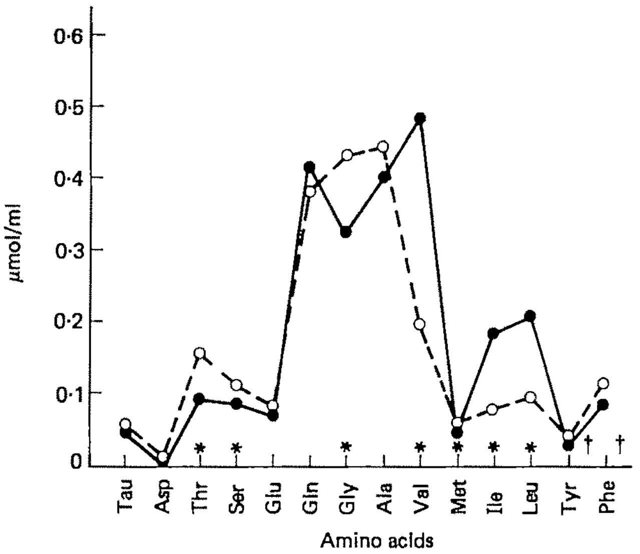

Figure 2 *Amino acid profile with the two infusions* ●, *50 per cent branched chain amino acids,* ○, *19 per cent branched chain amino acids,* *$P<0{\cdot}001$, †$P<0{\cdot}01$

($P<0{\cdot}001$) Phenylalanine (0·114±0·027 on AA and 0·085±0·014 μmol ml^{-1} on BCAA-TPN) and tyrosine levels (0·041±0·021 on AA and 0·028±0·015 μmol ml^{-1} on BCAA-TPN) were also significantly reduced on BCAA-TPN ($P<0{\cdot}01$). Serum concentrations of leucine (0·096±0·019 on AA and 0·208±0·047 μmol ml^{-1} on BCAA-TPN), isoleucine (0·077±0·019 on AA and 0·187±0·054 μmol ml^{-1} on BCAA-TPN) and valine (0·198±0·043 on AA and 0·485±0·136 μmol ml^{-1} on BCAA-TPN) were all significantly increased with the BCAA-TPN solution ($P<0{\cdot}001$). To discern whether these results could be explained in part by the nutritional status of the patients, regression analyses of the albumin synthetic rate to serum albumin, and tyrosine oxidation rate to weight loss were performed. There was no significant correlation between the patients' serum albumin and the fractional albumin synthetic rate ($r=0{\cdot}36$ for the AA infusion, $r=0{\cdot}18$ for the BCAA-TPN infusion). A strong, direct correlation between endogenous tyrosine oxidation rate and weight loss, however, was found with the BCAA-TPN infusion ($r=0{\cdot}79$) but not with AA infusion ($r=0{\cdot}01$). This suggests that those patients with greater weight loss were more catabolic. When taken in conjunction with the finding of a reduced tyrosine oxidation rate in the BCAA-TPN group, this suggests that the response to BCAA is related to nutritional status, with greater response in the better nourished

Discussion

It is well established that malnutrition from whatever cause leads to an increase in the morbidity and mortality rates from disease For this reason nutritional support has been used, particularly as an adjunct in the treatment of malignant disease. There is good evidence that preoperative TPN can improve perioperative morbidity and mortality rates in gastrointestinal cancer surgery and that this may in part be due to improved immunocompetence[22-24]. There is a debate however about whether conventional TPN reliably repletes body protein stores or improves long-term survival during oncological chemotherapy[23-25]. Owing to the unique metabolism of BCAA, it was felt that infusion of BCAA might act as a fuel source for the muscle and thereby limit net muscle protein breakdown in cancer cachexia Ultimately one might expect an improved clinical outcome of cancer chemotherapy if improved nutritional outcomes could be produced

A previous kinetic study with BCAA-TPN used [^{14}C]leucine as an isotope tracer[13]. This showed an increase in leucine flux, oxidation, synthesis, breakdown and balance as well as an increase in albumin synthetic rate. These were all significant except the leucine breakdown. Protein flux and oxidation would be expected to be increased by virtue of the increased dietary intake of leucine, but the changes in synthesis and balance were considered to be unbiased findings. However, there were concerns that the oxidation, although increased with BCAA-TPN, might be an underestimate due to oxidation occurring intracellularly rather than in the plasma where the flux measurements are made owing to the extracellular–intracellular gradient for leucine. Because of the concerns about whether distorted results might be obtained when greater quantities of leucine were found in one of the experimental diets, it was decided to confirm the results by employing [^{14}C]tyrosine as the primary tracer. [^{13}C]leucine was concomitantly infused, both to allow close comparison with previous studies and to estimate the *de novo* synthesis of tyrosine from phenylalanine. As the tracer [^{14}C]tyrosine is radioactive, it was not possible to use an additional radioactive isotope in humans. For this reason, [^{13}C]leucine, the naturally occurring stable isotope of leucine, was used. This may have some theoretical disadvantage, as in using this compound appreciable amounts exceeding 'tracer' quantities must be infused to obtain adequate samples for analysis

Using the tyrosine tracer, the flux was increased and oxidation decreased on BCAA-TPN. As neither solution (AA nor BCAA-TPN) contains significant amounts of tyrosine (1·8 per cent flux in BCAA-TPN and 3·8 per cent flux in AA), this presumably represents a true influence of the BCAA-TPN, the reduced oxidation reflecting an improvement in amino acid reutilization. The leucine tracer showed a significant increase in oxidation, but in this case it was felt to be due largely to the substantially increased concentration of leucine in the diet (32·4 per cent flux in BCAA-TPN and 19 per cent flux in AA) of the BCAA-TPN solution. Both tracers demonstrated an increase in flux with BCAA-TPN which must, by definition, be associated with an increase in breakdown and this was significant by the tyrosine tracer There is, however, a simultaneous increase in protein synthesis which can be attributed to the increased leucine concentration, perhaps reflecting leucine's role as a modulator of protein synthesis in muscle. An increase in the fractional albumin synthetic rate also strongly supports a positive benefit from BCAA-TPN.

In calculating the *de novo* synthesis of tyrosine from phenylalanine, using the leucine breakdown (×3·5/7·5) in the tyrosine equation, negative synthetic rates are obtained, which is clearly not possible In using this calculation it is assumed that both leucine and tyrosine remain in the same metabolic pool, are treated equally, and that the appearance of amino acids from protein breakdown are in exact proportion to their relative abundance in body protein. In this instance the amino acid distribution in the diet is distinctly different from the usual composition in body proteins. Since dietary intake makes such a large contribution to the whole body leucine flux, we might anticipate that there would not be a good correlation between the results determined by the two tracers. In fact, even though leucine and tyrosine tracers showed equivalent results, they did not correlate well and this must, at least in part, be due to the reason above None the less, in a qualitative sense, similar information would result whichever tracer was employed Thus leucine remains a useful tracer of protein kinetics in situations where the experimental diets are dissimilar in leucine content

The results of the amino acid profiles are of some interest. The reduced concentrations of phenylalanine, tyrosine, threonine, glycine, serine and methionine most likely reflect a lower concentration in the BCAA-TPN solution. The BCAA-TPN solution had no differential effect on taurine, aspartate, glutamate, glutamine and alanine Thus, despite the decrease in dietary intake, alanine levels were maintained by the BCAA-TPN solution Presumably this is due to the increased BCAA oxidation which would increase *de novo* alanine synthesis[26]. Glutamate and glutamine have been shown to be important factors in maintaining nitrogen balance[27] and glutamine plays an important role in the maintenance of the nutrition of the gastrointestinal trace, particularly enterocyte structure and function[28] The levels of both these amino acids were maintained on the BCAA-TPN solution even with the reduced intake. This is, once again, presumed to be due to increased *de novo* synthesis of glutamine with increased BCAA oxidation[26]. As expected the levels of leucine, isoleucine and valine were dramatically increased, confirming that the increased dietary intake leads to increased serum concentrations.

In summary, this study confirmed that an increase in BCAA in the diet leads to an increase in circulating plasma levels. These higher levels are the putative agent responsible for an increase in protein flux and breakdown, with a reduction in protein oxidation and an increase in protein synthesis and fractional albumin synthetic rate as determined by [^{14}C]tyrosine. These results confirm improved protein utilization with the BCAA-TPN solution as compared with the standard TPN solutions in cancer cachexia, with a suggestion that the response may be dependent on nutritional status. Whether these metabolic benefits of feeding a BCAA-enriched diet will translate into clinical benefit in cancer cachexia is unknown and uncertain. However, previous studies of parenteral feeding in cancer patients with standard formulae has been found to be less effective at protein repletion than in similarly malnourished patients without cancer[25]. Furthermore, parenteral feeding with standard formulae has not been shown to improve consistently clinical response or mortality in randomized trials employing TPN and chemotherapy[24]. BCAA-enriched TPN in cancer cachexia might be associated with benefits clinically, but randomized trials are necessary to explore these possibilities. With two positive studies of the value of BCAA in cancer cachexia in humans now available, perhaps the opportune time for such trials has arisen.

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Isotopic studies during surgical convalescence

We have performed paired isotopic studies in four patients undergoing resection of early colorectal cancer and four having removal of parathyroid adenomas. Kinetic measurements of protein and glucose metabolism were made before resection and at home 10 weeks after surgery. During convalescence there were major changes in both groups in glucose metabolism and the hormonal milieu despite no alterations in protein kinetics or metabolic rate. In particular, the rate of glucose production doubled from (mean ± s.e.m.) 14·8 ± 1·3 to 28·1 ± 2·5 μmol kg^{-1} min^{-1} ($P < 0{\cdot}01$), the percentage of available glucose undergoing oxidation decreased from 35·5 ± 3·9 to 21·5 ± 2·9 per cent ($P < 0{\cdot}05$) *and the percentage of glucose undergoing recycling to lactate increased from 20·1 ± 10·0 to 52·9 ± 2·3 per cent* ($P < 0{\cdot}05$). *During convalescence the basal plasma insulin concentration was significantly higher* ($P < 0{\cdot}05$) *and there was a proportionately smaller response to glucose infusion. The convalescent state was also associated with an elevation in serum cortisol from 291 ± 54 to 496 ± 75 nmol litre*$^{-1}$ *(*$P < 0{\cdot}05$*). The values for resting energy expenditure were not significantly different from the predicted energy expenditure in either the preoperative or the convalescent groups. We conclude that (a) there is a marked increase in both glucose production and glucose recycling to lactate in convalescence from clean uncomplicated surgery, and this is associated with a decrease in the percentage of glucose uptake oxidised; (b) a relative hyperinsulinaemia is seen in convalescent patients and is associated with decreased responsiveness to a glucose load; (c) the plasma cortisol level is significantly elevated after 10 weeks of convalescence; and (d) convalescent patients do not have elevated rates of protein catabolism or energy expenditure.*

Keywords: Convalescence, isotopes, recycling

D. A. Humberstone* and
J. H. F. Shaw

University Department of Surgery,
Auckland Hospital, Auckland,
New Zealand
Correspondence to:
Professor J. H. F. Shaw

The metabolic and hormonal response to various forms of stress, including operative trauma, has been extensively studied[1–3]. Not surprisingly, a large body of literature exists describing the aberrations that occur as a result of surgical stress. These include a pronounced neuroendocrine response with increased sympathetic nervous system activity combined with changes in catecholamine, glucagon, growth hormone and insulin levels[3–6]. These hormonal changes are associated with a host of metabolic changes: in particular, enhanced mobilization of fat[5,7], enhanced protein catabolism and nitrogen loss[8,9], decreased glucose tolerance[6,10] and enhanced glucose turnover[1].

Despite this evidence regarding the immediate response to stress and/or surgery, there is a relative scarcity of information on the hormonal and metabolic changes that occur during convalescence from major uncomplicated surgery. Rose and King[11] pointed out that, 'Although knowledge of the internal biochemical milieu in man after operations has increased, relatively little effort has been directed towards increasing the understanding of the adaptation of man postoperatively to his external environment, including the routine demands of everyday life.'

Clinicians dealing with patients during their convalescence often find that many report feelings of tiredness, listlessness and lethargy for weeks and occasionally months after surgery. A number of findings have been associated with the convalescent state. These include impaired muscle function[12], weight loss[13], alterations in anthropometric data[13], decreases in serum transferrin[13], and impaired adaptabilty of heart rate to submaximal work[14], and some researchers have suggested the importance of the degree of surgical trauma and the duration of anaesthesia as causative factors for fatigue after surgery[15].

Although it is likely that the physical symptoms occurring during convalescence have a metabolic and hormonal basis, as is the case with the immediate response to stress and surgical trauma[1], few if any studies have measured energy kinetics, metabolic rates or hormonal levels in convalescent patients after discharge. Because of the uncertainties regarding the metabolic abnormalities, if any, associated with the convalescent state, we have performed paired studies measuring glucose and protein kinetics, metabolic rates and hormonal levels both preoperatively and during convalescence. Each patient was studied before surgery and again some 10 weeks after discharge from hospital.

Patients and methods

Paired isotopic studies were performed on four patients with histologically proven Dukes' A or B[17] adenocarcinoma of the colon or rectum and four patients with primary hyperparathyroidism. All patients were recruited from the general surgery wards at Auckland Hospital. Informed written consent was obtained in all instances The study was approved by the Ethical Committee at Auckland Hospital and the use of radioisotopes was approved by the National Radiation Laboratory of New Zealand See *Table 1* for patient details.

Nutritional intake

All patients were at least 12 h postabsorptive when studied. Basal kinetics were first determined, then the effect of glucose infusion was assessed by infusing glucose at 4 mg kg^{-1} min^{-1} for 2 h

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* *Todd Foundation Fellow in Clinical Oncology*

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Table 1 *Patient details*

Patient	Age (years)	Sex	Weight (kg)	Diagnosis
CR_1	79	F	50	Dukes' B carcinoma of the sigmoid colon
CR_2	77	M	60	Dukes' B carcinoma of the rectum
CR_3	56	F	81	Dukes' A carcinoma of the rectum
CR_4	69	M	98	Dukes' B carcinoma of the descending colon
PTH_1	71	M	63	Primary hyperparathyroidism
PTH_2	66	M	70	Primary hyperparathyroidism
PTH_3	43	F	64	Primary hyperparathyroidism
PTH_4	26	F	69	Primary hyperparathyroidism

CR, colorectal group; PTH, parathyroid group

Study design

All patients were studied before surgical resection and again on average 10 weeks afterwards. The studies were of two types and each was of 5 h duration necessitating four studies for each patient, two before surgery and two in the convalescent stage During the first 3 h of the studies isotope only was infused (period 1) and during the 2 h of period 2 the isotopic infusion was maintained and, in addition, glucose was infused at 4 mg kg^{-1} min^{-1} The isotopes were infused through a cannula in a forearm vein using an IVAC pump (Ivac Corp, San Diego, California, USA) Multiple blood samples were taken from a contralateral limb vein using another cannula over the last 30 min of period 1 and again over the last 30 min of period 2. Samples of expired air were also collected during these sampling periods when glucose oxidation was being assessed The air was collected into 6-litre anaesthetic bags and sampled for $^{14}CO_2$-specific activity. This method involves trapping 1 mmol CO_2 in a solution of hydroxide of Hyamine (Rohm and Haas Company, Philadelphia, USA) with 1 per cent phenolphthalein solution added as an indicator to mark when the solution was saturated with CO_2. After this the resultant solution had scintillation cocktail added and was counted on a liquid scintillation counter.

Indirect calorimetry was also carried out at this time using a Sybron Taylor Oxygen Analyser (UK) and an ADC CO_2 analyser (Hoddesden, UK)

Isotopic infusions

Two different types of infusion were employed on separate days.

To assess glucose kinetics and glucose oxidation To assess glucose kinetics and glucose oxidation we obtained [^{14}C]glucose and [6-^{3}H]glucose from Amersham laboratories (Amersham, UK) and these were infused as a primed constant infusion. The infusion rate for each isotope was approximately 1 nCi kg^{-1} min^{-1} with a priming dose of 80·1. The study was of 5 h duration with an infusion of glucose being employed during the last 2 h of the study (period 2) at a rate of 4 mg kg^{-1} min^{-1}. The bicarbonate pool was primed with $NaH^{14}CO_3$ as described previously[18].

To assess protein kinetics and net protein catabolism. To assess protein kinetics and net protein catabolism, [^{14}C]urea was infused throughout. Period 1 was of 3 h duration and in period 2 a glucose infusion was employed as in the protocol described above The infusion rate for [^{14}C]urea was 1 2 nCi kg^{-1} min^{-1} with a prime of 540 nCi kg^{-1} We have described both of these methods previously[18]

Analysis of samples

Blood samples were centrifuged to separate the plasma which was immediately chilled [^{3}H]- and [^{14}C]glucose and [^{14}C]urea specific activities were determined as described elsewhere[18]. Plasma insulin assays were determined using a radioimmunoassay and the cortisol concentrations with an Amerlex Cortisol RIA kit (Amersham, UK).

Calculations

Energy expenditure. From the calorimetry data and details of the patients' height, weight, age and sex, two further values were calculated The predicted energy expenditure (PEE) was calculated using the revised Harris–Benedict formula[19]. For male patients: PEE(kcal 24 h^{-1} = 5(height) + 13·7(weight) + 66 − 6·8(age), and for female patients· PEE(kcal 24 h^{-1}) = 1·85(height) + 9 6(weight) + 655 − 4·7(age).

The resting energy expenditure (REE) was calculated using the method of Weir[20]· REE(kcal 24 h^{-1} = 1440 min × (3 9 × V_{O_2} + 1·1 × V_{CO_2})

Isotopic calculations. The rate of appearance of glucose (Ra glucose) and Ra urea were calculated using the Steele equation as it applies to isotopic steady state[21]

$$\mathrm{Ra} = \frac{\text{infusion rate}}{\text{specific activity (SA)}} \tag{1}$$

Glucose oxidation (GO) was calculated as follows:

$$\mathrm{GO} = \frac{^{14}\mathrm{CO}_2 - \mathrm{SA} \times V_{\mathrm{CO}_2}}{[^{14}\mathrm{C}]\text{glucose} - \mathrm{SA} \times \mathrm{K}} \tag{2}$$

The percentage of glucose recycling was calculated as follows·

$$\text{percentage recycling} = \frac{\mathrm{Ra}(^{3}\mathrm{H} - {}^{14}\mathrm{C})}{\mathrm{Ra}(^{3}\mathrm{H})} \times 100 \tag{3}$$

The percentage of glucose uptake oxidized (GUO) was calculated as follows.

$$\mathrm{GUO} = \frac{\text{Glucose oxidation}}{\text{Ra glucose}} \times 100 \tag{4}$$

Net protein catabolism is derived from the Ra urea data and expressed as grams of protein per kilogram per day.

This methodology has been described elsewhere[18] including the calculation of the constant, K (equation 2)

Statistical analysis

The data obtained from the patients before surgical resection were compared with the convalescent data using the Mann–Whitney *U* test. The basal data in each study were compared to the corresponding data during glucose infusion also using the Mann–Whitney *U* test.

Results

As the basal values for both the colorectal and the parathyroid patients were similar, and the same trends were seen over 10 weeks of convalescence in both groups, the data have been pooled in this section for statistical analysis. However the raw data for each group can be seen in *Tables 2* and *3*, both in the basal state and during convalescence.

Energy expenditure

The PEE for the preoperative patients was 188 ± 7 kcal 24 h^{-1} (mean ± s.e.m.) and for the convalescent group it was 1360 ± 64 kcal 24 h^{-1}. The mean REE in the preoperative group was 1194 ± 62 kcal 24 h^{-1} which was not significantly different from the value obtained in the convalescent group: 1260 ± 46 kcal 24 h^{-1}.

Glucose metabolism

The basal rate of glucose production in the preoperative group was 14·8 ± 1·3 μmol kg^{-1} min^{-1} (mean ± s.e.m.) and following glucose infusion there was a 66·6 ± 12·2 per cent suppression of endogenous Ra glucose to 5·0 ± 0·4 μmol kg^{-1} min^{-1}. In contrast, in the convalescent patients the basal Ra glucose was significantly higher at 28·1 ± 2·5 μmol kg^{-1} min^{-1}/($P < 0·01$) and following glucose infusion there was a significantly smaller suppression of endogenous glucose production ($P < 0·05$) at 35·6 ± 5·6 per cent, resulting in an endogenous Ra glucose of 18·1 ± 1·7 μmol kg^{-1} min^{-1}. The percentage of glucose uptake oxidized in the preoperative patients was 35·5 ± 3·9 per cent. However, in the convalescent patients the percentage of glucose undergoing oxidation was significantly less at 21·5 ± 2·9 per cent ($P < 0·05$). Glucose recycling was 20·1 ± 10·0 per cent in the preoperative group. In the convalescent patients the percentage of glucose underging recycling was significantly higher at 52·9 ± 2·3 per cent ($P < 0·01$). See *Table 4* for details of glucose metabolism.

Urea kinetics and net protein catabolism

The mean (± s.e.m.) Ra urea in the preoperative patients was 8·0 ± 2·8 μmol kg^{-1} min^{-1}. The corresponding value in the same patients some 10 weeks later was not significantly different at 8·3 ± 1·7 μmol kg^{-1} min^{-1}. When net protein catabolism (NPC) was calculated from these data the preoperative NPC was

Table 2 *Data summary of colorectal patients*

	Preoperative	Convalescent	Reference range[16]
Ra glucose (μmol kg^{-1} min^{-1})	12·6±1·0	29·5±5·0*	13·3±0·2
Glucose oxidized (%)	39·7±4·4	19·6±3·7*	32·8±2·0
Glucose recycled (%)	4·3±2·2	50·1±2·4*	12±2
Glucose clearance (ml kg^{-1} min^{-1})	2·4±0·3	5·2±0·8*	2·6±0·2
Suppression DGI (%)	81·4±6·8	41·3±5·3*	76±6
Ra urea (μmol kg^{-1} min^{-1})	5·3±0·3	5·8±0·2	5·2±0·2
Net protein catabolism (g kg^{-1} day^{-1})	1·3±0·07	1·5±0·06	1·3±0·03
Plasma insulin (microunits litre^{-1})	0·3±0·3	16·8±4·4*	
Plasma cortisol (nmol litre^{-1})	333±56	538±79*	

Ra glucose, glucose production; suppression DGI, percentage suppression of endogenous glucose turnover during glucose infusion; Ra urea, urea production; *, significantly different from the corresponding value in the preoperative group

Table 3 *Data summary of parathyroid patients*

	Preoperative	Convalescent	Reference range[22]
Ra glucose (μmol kg^{-1} min^{-1})	17·1±1·9	26·8±1·8*	14·4±1·5
Glucose oxidized (%)	37·0±4·1	26·1±5·0*	31·3±3
Glucose recycled (%)	42·2±2·3	59·0±1·0*	
Glucose clearance (ml kg^{-1} min^{-1})	3·4±0·4	5·4±0·4*	3·0±0·5
Suppression DGI (%)	56·5±3·5	11·3±4·2*	
Ra urea (μmol kg^{-1} min^{-1})	9·9±4·7	10·6±1·8	8·5±2·0
Net protein catabolism (g kg^{-1} day^{-1})	2·5±1·2	2·7±0·5	2·1±0·3
Plasma insulin (microunits litre^{-1})	10·3±3·0	19·3±4·2*	
Plasma cortisol (nmol litre^{-1})	243 ±35	393 ±66*	

Ra glucose, glucose production; suppression DGI, percentage suppression of endogenous glucose turnover during glucose infusion; Ra urea, urea production; *, significantly different from the corresponding value in the preoperative group

Table 4 *Summary of glucose metabolism*

	Preoperative	Convalescent
Ra glucose (μmol kg^{-1} min^{-1})	14·8± 1·3	28·1±2·5*
Endogenous Ra glucose DGI (μmol kg^{-1} min^{-1})	5·0± 0·4	18·1±1·7*
Suppression DGI (%)	66·6±12·2	35·6±5·6*
Glucose oxidized (%)	35·5± 3·9	21·5±2·9*
Glucose recycled (%)	20·1±10·0	52·9±2·3*
Glucose clearance (ml kg^{-1} min^{-1})	2·9± 0·3	5·3±0·4*

Ra glucose, glucose production; endogenous Ra glucose DGI, endogenous glucose produced during glucose infusion of 4 mg kg^{-1} min^{-1}; suppression DGI, percentage suppression of endogenous glucose turnover during glucose turnover; *, significantly different from the corresponding value in the preoperative group

Table 5 *Plasma hormones during convalescence*

	Preoperative	Convalescent
Plasma insulin (microunits litre^{-1})	3·2±2·3	14·0±3·8*
Plasma insulin DGI (microunits litre^{-1})	22·4±4·0	22·0±4·2
Plasma cortisol (nmol litre^{-1})	291±54	496±75*

Plasma insulin DGI, plasma insulin during glucose infusion; *, significantly different from the corresponding preoperative value

2·0±0·7 which is not significantly different from the convalescent value of 2·1±0·4 g kg^{-1} day^{-1}.

Plasma hormonal measurements

The mean (±s.e.m.) preoperative plasma insulin level was 3·2±2·3 microunits litre^{-1} and following glucose infusion this increased to 22·4±4·0 microunits litre^{-1} ($P<0{\cdot}01$) In the convalescent patients the basal insulin level was significantly higher ($P<0{\cdot}05$) at 14·0±3·8 microunits litre^{-1}. After glucose infusion in convalescent patients there was a proportionately smaller increase in plasma insulin to 22·0±4·2 microunits litre^{-1} ($P<0{\cdot}05$). The plasma insulin concentration during glucose infusion was not significantly different between the two groups.

Preoperatively the plasma cortisol concentration was 291±54 nmol litre^{-1} (mean±s.e.m.). The corresponding value in the convalescent patients was significantly higher at 496±75 nmol litre^{-1} ($P<0{\cdot}5$) (*Table 5*).

Discussion

The aim of our study was to define the metabolic profile of convalescent surgical patients and we have successfully documented a few of the probable myriad of changes occurring in these patients. The study groups were chosen because both were to have operative procedures of a similar duration although each had clearly differing degrees of tissue trauma It was our contention that if the convalescent state was associated with altered metabolic parameters then these would be relatively independent of the degree of tissue trauma. By seeing similar results in two groups with marked differences in tissue trauma we have excluded this as a variable.

Intuitively, both groups would be expected to benefit from surgery in a clinical sense, one because a malignant condition was being resected, the other because a functional adenoma resulting in symptomatic hypercalcaemia was being resected. It is important to note that the same trends were seen in both groups of patients. Although the sample number in both groups is relatively small it is reassuring to note that the preoperative data obtained in both the colorectal and parathyroid patients were similar to those we have previously published in larger series of patients These data can be seen in *Tables 2* and *3* and are obtained from References 16 and 22.

The metabolic rate in these patients was not greatly different from the predicted value, either before surgery or during convalescence. This is in accord with the work of Dempsey *et* *al.*[23] and findings of our own[16]. These data suggest that the patient with early colorectal cancer has a low or normal metabolic rate and we have previously shown patients with hyperparathyroidism to be normometabolic[22]. In addition, it is known that the basal metabolic rate does not change after moderately traumatic but uncomplicated surgery[24]. The slight decrease in predicted energy expenditure from preoperative to convalescent patients can be explained on the basis of the minor weight changes that occurred over this period. Metabolic rate is also a useful measure of surgical 'stress' and it is reassuring to note that during the study period the patients were normometabolic, that is we can deduce that the study itself was not associated with significant 'stress'.

Our key findings revolve around the marked alterations in glucose metabolism occurring in the convalescent setting. Glucose metabolism has been extensively studied in various conditions[16,18,22,25–27] and our present study documents major aberrations in glucose utilization. In particular, the convalescent patient appears to be unable to completely oxidize glucose to CO_2 and this is coupled with an increase in glucose recycling to lactate. Glucose oxidation decreases by approximately 40 per cent whereas glucose recycling more than doubles. This finding is consistent with the work of others who have demonstrated increased lactate production during convalescence[28]. The importance of this finding is that glucose recycling to lactate with subsequent Cori recycling is an energy-expensive process. Every 1 mol glucose metabolized to pyruvate/lactate yields 4 mol ATP. However, for that lactate to be metabolized back to glucose via the Cori cycle requires an additional 6 ATP resulting in a net energy imbalance. It is also important to realize that these changes are occurring in an essentially anaerobic part of metabolism and thus may not be reflected in an increased oxygen consumption. Furthermore, this finding of impaired glucose oxidation coupled with enhanced recycling is similar to what is seen in other forms of stress. For example, we have previously shown that severely septic patients have impaired glucose oxidation and enhanced substrate recycling[29], and Burke *et al.*[27] have demonstrated similar findings in traumatized patients.

The plasma cortisol concentrations were significantly higher in the convalescent patients, compared with the corresponding preoperative values, although on both occasions they were within the reference range quoted by our laboratory. All blood samples for cortisol assay were taken at the same time on each day of the study to allow for the diurnal rhythm of cortisol secretion. It is hard to determine how much emphasis to place on these cortisol results. The actions of cortisol are known to include: increased protein catabolism[30], increased hepatic glycogenolysis[31,32], increased gluconeogenesis[30] and increased Cori cycling[31,32]. In addition, cortisol is known to have an anti-insulin effect. It is likely that cortisol could be implicated in some of the observed changes seen in glucose metabolism as well as the diminished responsiveness of insulin secretion to glucose infusion seen in the convalescent patients.

The stimulus for the high basal insulin concentration seen in the convalescent patients is probably related, in part, to the elevated rates of glucose production in these patients. However, despite this elevated insulin concentration, the plasma glucose level was higher in the convalescent group, suggesting decreased insulin effectiveness. This finding of decreased effectiveness is consistent with what is seen in other forms of stress such as sepsis[29].

In summary, our data demonstrate that convalescent patients are metabolically abnormal 10 weeks after surgery. They have abnormalities in glucose metabolism and hormonal profile independent of changes in metabolic rate and protein metabolism. Inefficient pathways are prominent in these patients. In particular, there is an increase in anaerobic energy-expensive metabolism (glucose recycling) at the expense of oxidative aerobic metabolism. There are changes in stress hormone secretion and it is likely that the high cortisol concentration and decreased insulin secretory responsiveness are important in mediating the above changes. In contrast to what has been suggested by others, we have observed these abnormal findings in patients 10 weeks after surgery when all patients are managing at home independently. Metabolic changes following surgery appear to be unrelated to the degree of surgical trauma as evidenced by the similar changes seen in two different groups of patients.

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Case reports

Br. J. Surg. 1989, Vol. 76, February, 158–159

Free-flap reconstruction of heel pad after femorotibial bypass salvage graft

R. J. McFarland, R. S. Taylor, F. Wood* and B. Mayou*

*Department of Surgery, Epsom District Hospital, Surrey and *Department of Plastic Surgery, St. Thomas' Hospital, London SE1, UK*

Correspondence to: Mr R. J. McFarland, Department of Surgery, St. George's Hospital, Blackshaw Road, London SW17 0QT, UK

The presence of full-thickness ischaemic necrosis of the heel with extensive exposure of the calcaneum has long been regarded by most surgeons as an indication for amputation. We describe such a patient in whom an aggressive team approach by vascular and plastic surgeons enabled the heel pad to be restored using microvascular surgical techniques.

Case report

A 78-year-old Polish man, who had been a lifelong smoker, had suffered progressive intermittent claudication in his right leg for 5 years. Nine months previously he had been investigated elsewhere, deemed unsuitable for vascular reconstruction, and had undergone lumbar sympathectomy without benefit.

When referred he could walk only a few yards and had developed a large painful ischaemic ulcer on his heel which was infected and necrotic, with exposed bone. The right femoral pulse was present but no distal pulses were palpable. Doppler studies showed an anterior tibial arterial pressure of 35 mmHg (pressure index 0·24) and no posterior tibial artery signal. Arteriography showed the superficial femoral artery to be blocked at the origin with occlusion of the popliteal artery both above and below the knee joint. The profunda femoris artery was patent but diseased and fed a number of small collaterals about the knee. The anterior tibial artery appeared to be patent throughout; the posterior tibial artery was patent but diseased in the distal part of its course and the peroneal artery was occluded.

Vascular reconstruction

Initially a graft to the anterior tibial artery was attempted as all investigations suggested that this was the most suitable recipient vessel. Accordingly, the anterior tibial artery was exposed via a lateral approach excising a segment of the fibula. However, the vessel appeared very diseased and when the arteriotomy was made there was almost no back bleeding and a fine 1 mm Parsonnet probe would not pass more than 7 cm distally. The posterior tibial artery was explored and found to be patent from a point 3 cm below its origin, accepting a 2 mm probe to a level just above the ankle. A 6 mm ringed polytetrafluoroethylene (PTFE) graft (GORE-TEX®, W. L. Gore and Associate, Incorporated) was placed in a subcutaneous tunnel and anastomosed to the common femoral artery in the groin and to the posterior tibial artery using our standard technique, which incorporates a vein gusset into both proximal and distal anastomoses. An operative arteriogram showed the anastomosis to be satisfactory and confirmed patency of the artery to the ankle.

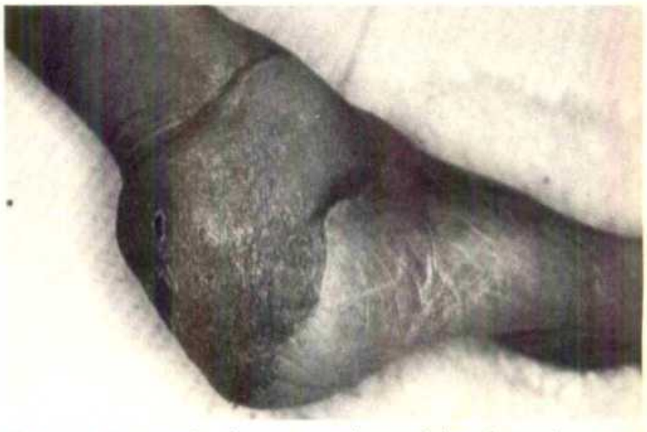

Figure 1 *Five months after surgery the arterial graft remains patent and the skin flap is healthy*

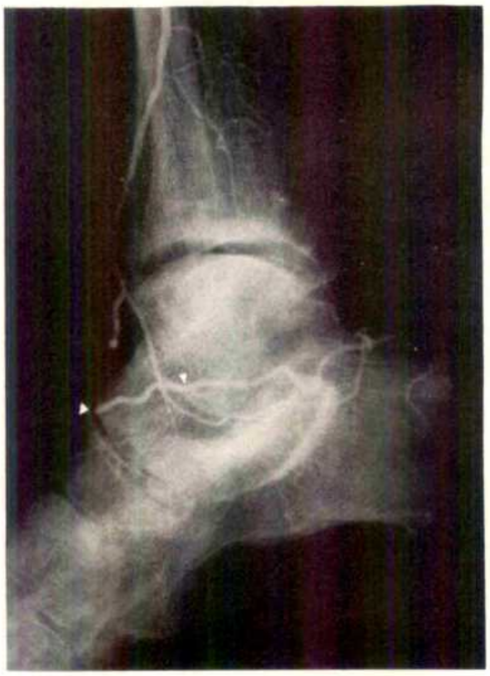

Figure 2 *Arteriogram at 6 months shows the radial artery supplying the skin flap (arrowed) taking origin from a dorsalis pedis artery which is filled retrograde from a vascular reconstruction to the posterior tibial artery*

Postoperatively, Doppler pressures were 80 mmHg in the posterior tibial and 130 mmHg in the dorsalis pedis (pressure indices 0·57 and 0·93, respectively) despite the latter vessel filling only indirectly through collaterals.

Plastic reconstruction

Although the fore-foot now appeared viable there was such extensive soft-tissue necrosis of the heel pad that after débridement the ulcer

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measured 17 × 8 cm and the weight-bearing area of the calcaneum was exposed. Owing to the size and depth of the ulcer, full-thickness tissue replacement was felt to be necessary. Local flaps were small and the vascular supply in doubt; therefore, a free vascularized radial forearm flap was planned.

Five weeks after the vascular reconstruction the ulcer was stable and arteriography confirmed a patent graft with filling of the anterior tibial vessels.

A left radial forearm flap, 18 × 9 cm, was raised, and transferred to the right heel. An end-to-side anastomosis was performed between the radial artery and the dorsalis pedis artery, and end-to-end anastomoses were performed with both venae communicantes, using microsurgical techniques.

One month later the flap was trimmed and inset. Healing was complete at 6 weeks and the patient could be mobilized, taking full weight on his heel.

After 5 months the vascular graft was still patent and the foot, including the heel flap, was healthy and pain free (*Figure 1*). While the patient was being investigated for severe claudication in his other leg, the arteriogram shown in *Figure 2* was obtained. This shows the PTFE graft to the posterior tibial artery supplying the foot vessels and from these the dorsalis pedis artery from which the skin flap artery takes origin.

Discussion

A functioning vascular graft is of no value if the patient cannot walk on the salvaged foot. In our experience, patency rates of 90 per cent at 1 year can be obtained using externally supported PTFE prosthetic grafts to a suitable tibial or peroneal vessel provided that vein patches are incorporated in the anastomoses. The patch may be beneficial in reducing the compliance mismatch between prosthesis and artery, perhaps leading to increased flow, and reducing the severity of intimal hyperplasia. We believe that, in the absence of severe established gangrene, amputation should never be performed without first exploring the tibial vessels. As this case demonstrates, the arteriogram may not always give a true picture of the distal vessels. Even so, until recently this man's foot would have been regarded as unsalvageable as traditional skin grafts are not sufficiently robust to cover exposed bone on a weight-bearing area.

The free-flap technique provides substantial skin cover of even large areas of exposed bone without lengthy immobilization. The best source vessel in the foot is the anterior tibial as it is superficially situated and therefore accessible for the end-to-side placement of a 'wrap-around' graft for heel or sole. In our patient, even though the vascular graft was to the posterior tibial, the collateral flow to the dorsalis pedis artery was sufficient to support the flap.

In conclusion, the development of free-flap grafts means that extensive heel-pad necrosis should no longer be regarded as an indication to amputate. A distal vascular reconstruction which is successful in salvaging the rest of the foot can support a free-flap skin/muscle graft.

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Treatment of a postoperative cholecystocutaneous fistula by an endoscopic stent

M. L. Sedgwick and M. E. Denyer

Gastrointestinal Unit, Seacroft Hospital, York Road, Leeds LS14 6UH, UK

Correspondence to: Dr M. E. Denyer

Gallstone retention and external biliary fistulae are important complications following biliary surgery and cause significant morbidity and mortality. We describe a patient with a cholecystocutaneous fistula associated with a retained common bile duct stone who was successfully treated by endoscopic papillotomy and insertion of a biliary endoprosthesis.

Case report

A 76-year-old man was admitted in August 1986 with acute cholecystitis. Ultrasonography revealed several stones in the gallbladder which was dilated with an impacted stone at the neck. He had a history of recent myocardial infarction, so surgery was felt to be inadvisable. Clinically he settled well with conservative management.

In March 1987 he was readmitted with a history of passing dark urine for 2 weeks and severe upper abdominal pain for 1 day. He was tender in the right hypochondrium and became jaundiced shortly after admission. Initially he was managed conservatively but 3 days after admission his white cell count had risen to $14{\cdot}6 \times 10^6$/l, with bilirubin 157 μmol/l (ULN* 19), alkaline phosphatase 350 international units (ULN 85) and AST* 46 units/l (ULN 35), and he underwent laparotomy.

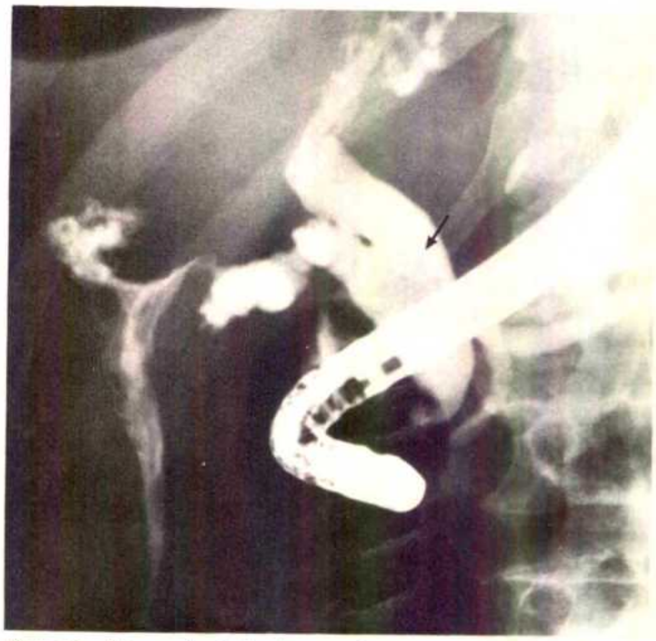

Figure 1 *Retrograde cholangiogram showing large common bile duct stone (arrowed) and cholecystocutaneous fistula*

A right paramedian incision revealed an inflammatory omental mass at the porta hepatis involving the first part of the duodenum and pylorus. A trial dissection failed to identify recognizable biliary anatomy; no bile leakage was noted. The abdomen was closed with a corrugated drain. Postoperatively his jaundice settled but he developed an external biliary fistula along the drain track, draining up to 500 ml of bile per day. This continued and 16 days postoperatively he was referred for endoscopic retrograde cholangiography (ERC), which showed a stone in the common bile duct impacted above the sphincter of Oddi and a cholecystocutaneous fistula (*Figure 1*). An adequate sphincterotomy was performed but the stone could not be extracted. Over the next week bile continued to drain via the fistula at a rate of 300–800 ml/day.

A repeat ERC showed that the stone had passed. To bypass the biliary leak a 10 Fr endoprosthesis 9 cm long was inserted endo-

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***** *ULN, upper limit of normal; AST, aspartate aminotransferase*

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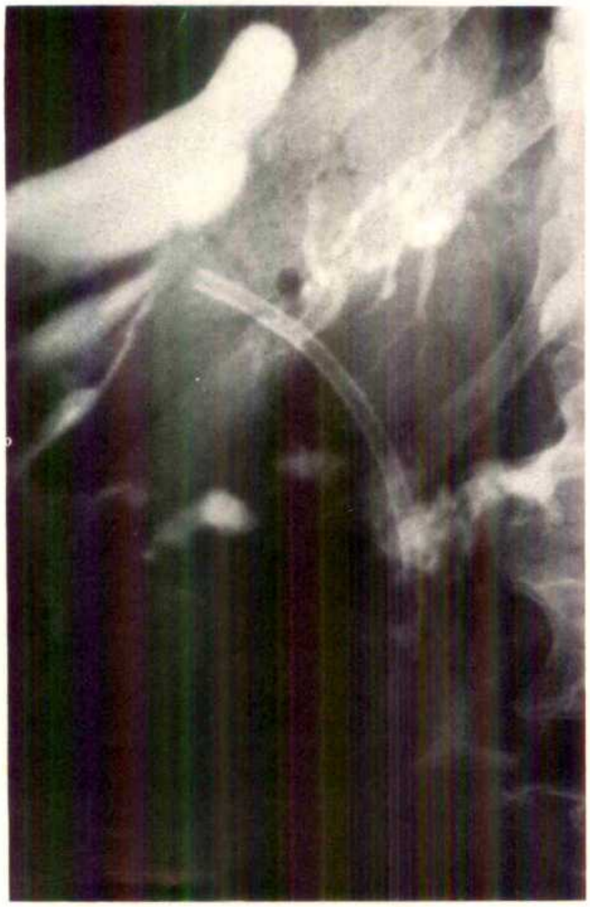

Figure 2 *Endoprosthesis inserted endoscopically with its proximal end above the cystic duct and distal end in the duodenum*

scopically with its proximal end above the cystic duct (*Figure 2*). There were no complications. Over the next 4 days the fistula dried up completely and his general condition improved. He was discharged home 1 week after insertion of the endoprosthesis. He remains well 1 year later, with no further jaundice or abdominal pain and no recurrence of his biliary leak.

Discussion

Biliary tract surgery is common and complications necessitated reoperation in 4·7 per cent of cases in one series, with considerable morbidity and mortality[1]. Of those cases requiring reoperation, 25 per cent have retained or recurrent biliary stones[1]. Biliary leaks are less common but are associated with higher morbidity and mortality.

Endoscopic sphincterotomy is an established method for removing retained stones with a 90 per cent success rate, a morbidity of 7–9 per cent and a mortality rate of 1 per cent or less[2]. Sphincterotomy has also been used successfully to treat postoperative external biliary fistulae[3]. Endoscopic stents have been of help in patients with post-cholecystectomy biliary–cutaneous fistulae[4,5] but not, to our knowledge, in patients with an intact gallbladder. The majority of enterocutaneous fistulae will close spontaneously provided that there is no distal obstruction. In our case a high-output fistula persisted after relief of the common bile duct obstruction by endoscopic sphincterotomy but resolved rapidly after insertion of a biliary endoprosthesis.

Acknowledgements

We would like to thank Mr V. J. Modgill for his permission to report this case.

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Reticuloendothelial failure in chronic intra-abdominal sepsis: the role of opsonic fibronectin

S. Cheslyn-Curtis,
M. C. Aldridge and
H. A. F. Dudley

Academic Surgical Unit, Queen Elizabeth The Queen Mother Wing, St. Mary's Hospital, London W2 1NY, UK

Correspondence to:
Miss S. Cheslyn-Curtis, Wexham Park Hospital, Slough SL2 4HL, UK

Severe sepsis leads to depression of the reticuloendothelial (RE) system with delayed bloodstream clearance of particulate matter and bacteria. Fibronectin may be an important opsonin of the RE system and low fibronectin levels often accompany severe sepsis in man. We have investigated the effect of prolonged intra-abdominal sepsis on plasma fibronectin concentrations and RE function. Serial plasma fibronectin concentrations were determined in rabbits for 2 weeks after either the induction of sepsis (appendix abscess) (n = 6) or laparotomy only (n = 6). RE function was measured at 2 weeks by determining the clearance kinetics and organ distribution of low dose technetium tin colloid (TTC). There was an early transient depression in plasma fibronectin values followed by elevated concentrations at 48–72 h which were more marked in the sepsis group. There was a delay in the blood clearance with reduced hepatic and increased bone uptake of TTC. We conclude that depletion of opsonic fibronectin is unlikely to be an important factor contributing to the impairment of RE function associated with intra-abdominal sepsis and that RE depression in septic animals is due to intrinsic Kupffer cell dysfunction.

Keywords: Fibronectin, reticuloendothelial function, intra-abdominal sepsis, intra-abdominal abscess

Sepsis remains a major cause of morbidity and mortality in surgical patients. The recent recognition of host defence failure and in particular that of the reticuloendothelial (RE) system during sepsis has generated interest in the underlying mechanisms. Failure of the RE system occurs during sepsis and may be due to several factors, including a deficiency of opsonins, an alteration in hepatic blood flow or intrinsic macrophage dysfunction. Fibronectin may be an important non-specific opsonin for the clearance of blood-borne particulate matter and bacteria and may play a protective part in conjunction with the RE system against microembolism of damaging particles (circulating bacteria and products of sepsis or tissue injury) which ultimately lead to end organ failure[1]. The demonstration of reduced fibronectin values during sepsis has led to trials of replacement therapy which have shown restoration of opsonin levels but have failed to show a significant improvement in survival[2]. Fibronectin concentrations have been raised in animal models of acute sepsis[3–5]. These severe models of sepsis have a very high early mortality and differ from the often slower, more insidious, onset of sepsis in surgical patients.

Low dose technetium tin colloid (TTC) can be used as an RE test agent to detect depression of RE-dependent blood clearance in the rabbit[6,7]. The aims of this study were to determine the effect of prolonged sepsis on plasma fibronectin concentrations and RE function, using a rabbit model of chronic intra-abdominal sepsis.

Materials and methods

Animal groups

Male New Zealand White rabbits (2·5–3·0 kg) were used.

Septic model. An intra-abdominal abscess was induced in the rabbit by devascularization of 80–90 per cent of the appendix. Animals were anaesthetized with intravenous sodium pentobarbitone (May and Baker Ltd., Dagenham, UK) and a midline laparotomy performed. The arcade of vessels between the appendix and small bowel and the main appendicular artery and vein were ligated and divided. The appendix was left *in situ* and the abdomen closed. Six animals underwent laparotomy only and acted as controls.

Measurement of plasma fibronectin

Blood was taken for plasma fibronectin estimation preoperatively, and postoperatively at 2, 4, 6, 9, 12, 15 and 24 h, and at 2, 3, 4, 6, 11 and 14 days. Blood was collected into paediatric size ethylene diaminetetraacetic acid polystyrene tubes, centrifuged immediately and the plasma removed for storage at −70°C. Plasma fibronectin concentrations were assayed by an immunoturbidimetric method[8] using commercially available antiserum. The results are expressed as the percentage change from the control (preoperative) value for each animal.

Measurement of RE function

RE function was measured 2 weeks after either laparotomy only or devascularization of the appendix. The rate of clearance of TTC from the bloodstream and its uptake into the liver, spleen, lungs and bone were determined. Animals were lightly anaesthetized with intravenous sodium pentobarbitone and a 1 ml bolus of TTC (Amerscan Hepatate II, Amersham International plc, Amersham, UK) was injected rapidly via an ear vein. The dose of TTC was approximately 0·0002 mg/kg labelled with 3·7 MBq technetium-99m. Serial blood samples were taken over 45 min from a vein in the contralateral ear. The animal was killed with an overdose of anaesthetic and the liver, spleen, right femur and lungs were removed. The activity of the blood and organs was measured using an LKB-Wallac 80 000 γ counter (LKB Instruments Ltd., Selsdon, South Croydon, UK). Blood clearance curves were constructed and analysed using a Hewlett Packard desk-top computer (HP9845B; Hewlett Packard, Wokingham, UK) running a pharmacokinetic program, modified to correct for radioactive decay and incorporating statistical analyses. The half-life of the clearance of TTC from the bloodstream was calculated from the first and fastest component of clearance. Uptake of TTC by the organs was measured by counting aliquots of homogenized liver and lung, and the whole spleen and right femur in the γ counter using 1 ml of TTC as a standard. The results are expressed as a percentage of the injected dose per gram of tissue.

Bacteriological cultures

Blood was taken for culture at 24 h and 14 days after operation.

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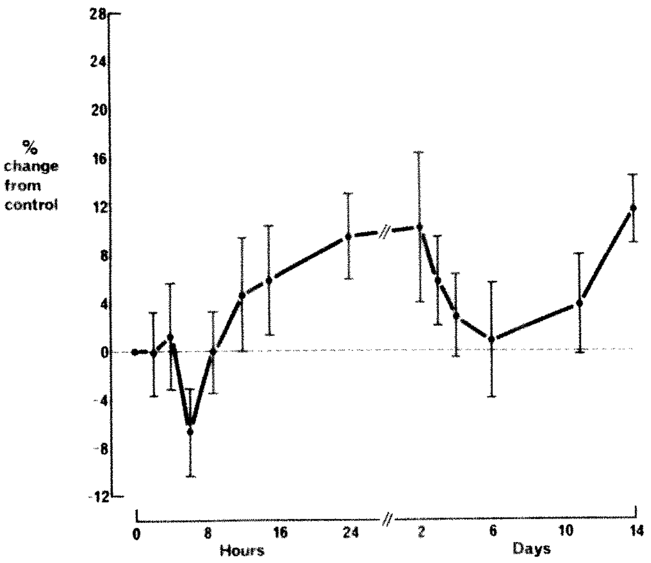

Figure 1 *Serial changes in plasma fibronectin concentrations in the laparotomy only group. The mean ± s.e.m. values are shown*

Cultures from the intra-abdominal abscess or peritoneum (laparotomy only animals) were taken when the animal was killed.

Statistical analysis

Results are expressed as the mean and standard error of the mean. Significance is tested by the Wilcoxon matched pairs signed rank or Mann–Whitney *U* test.

Results

The post-mortem finding in all the animals in the sepsis group was a solitary intra-abdominal abscess occupying the site of the appendix, surrounded by dense adhesions to other organs. Approximately 1 cm of the base of the appendix remained and appeared normal.

Bacteriology

In the sepsis group, five of six blood cultures taken at 24 h after the induction of sepsis were positive and grew a mixture of organisms. All blood cultures were negative at 14 days indicating that bacteriologically the sepsis was localized. Single species of bacteria were cultured from the pus in the intra-abdominal abscesses (*Escherichia coli*, $n=4$, and *Streptococcus faecalis*, $n=2$). All the blood and peritoneal cultures in the laparotomy only group were negative.

Plasma fibronectin

The plasma fibronectin results for the laparotomy only and sepsis groups are shown in *Figures 1* and *2* respectively. In the laparotomy only group (*Figure 1*), there was an initial depression in plasma fibronectin concentrations followed by an increase which reached a plateau at 24–48 h. After 1 week, plasma fibronectin concentrations had returned to normal but became elevated again at the end of the second week. In the sepsis group (*Figure 2*), there was a similar initial depression followed by a more marked increase in plasma fibronectin concentrations which did not peak until 72 h after the induction of sepsis. Plasma fibronectin concentrations returned to normal at the end of the first week but rose again during the second week.

The results for both groups are superimposed in *Figure 3* to illustrate the difference between the response to trauma and sepsis. The pattern of change in plasma fibronectin concentrations is similar for the two groups but the elevation occurring at 72 h in the sepsis group was significantly greater than the 48 h peak in the laparotomy only group ($P < 0.05$). The rise in plasma fibronectin during the second week was not statistically significant for either group.

Clearance kinetics

The clearance of TTC from the bloodstream is shown in *Figure 4*. There was a significant delay in the blood clearance of TTC in the sepsis group, as shown by the increase in the half-life.

Organ distribution

The distribution of TTC to the liver, spleen, bone and lungs is shown in *Figure 5a–d*. In the sepsis group, there was a reduction in the uptake of TTC by the liver but a significant increase in its uptake in bone. There was no difference between the two groups for the splenic uptake of TTC. Pulmonary localization of TTC was increased in the sepsis group, although this failed to reach statistical significance using the two-tailed Mann–Whitney *U* test.

Discussion

The results of this study demonstrate that there is an initial reduction in the concentration of plasma fibronectin after both surgical trauma and the induction of sepsis. This is a common finding in animals and man and occurs within hours of trauma. A reduction in plasma fibronectin concentrations has been found in the rat within 1 h of surgical (laparotomy and enterotomy)[9] or mechanical (Noble Collip drum) trauma[10] and

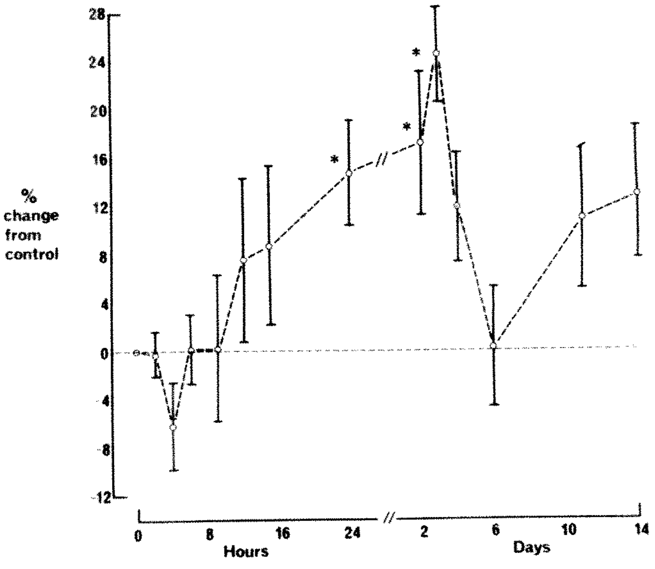

Figure 2 *Serial changes in plasma fibronectin concentrations in the sepsis group. The mean ±s.e.m. values are shown.* * $P<0.05$. *Wilcoxon matched pairs signed rank test*

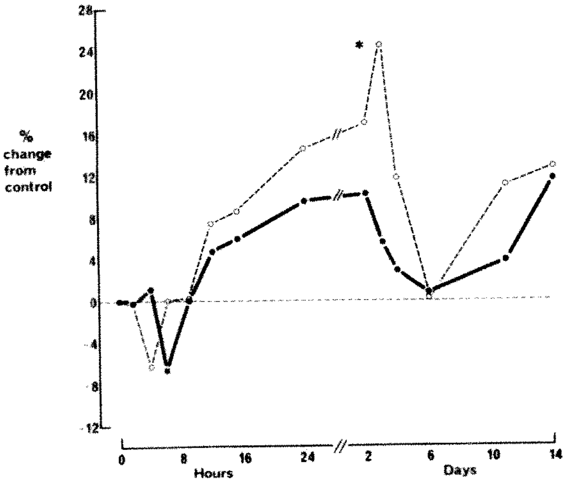

Figure 3 *Serial changes in plasma fibronectin concentrations in the laparotomy only* (●) *and sepsis* (○) *groups. The mean values only are shown.* * $P<0.05$. *Mann–Whitney* U *test*

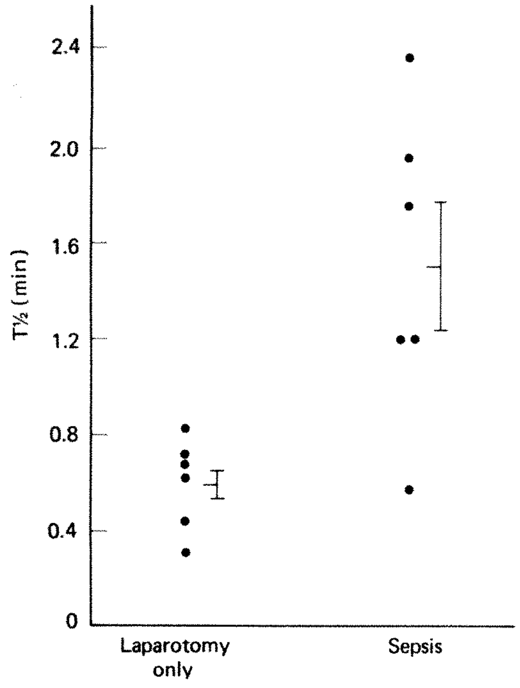

Figure 4 *Rate of blood clearance of low dose technetium tin colloid.* $P<0{\cdot}05$, *Mann–Whitney* U *test*

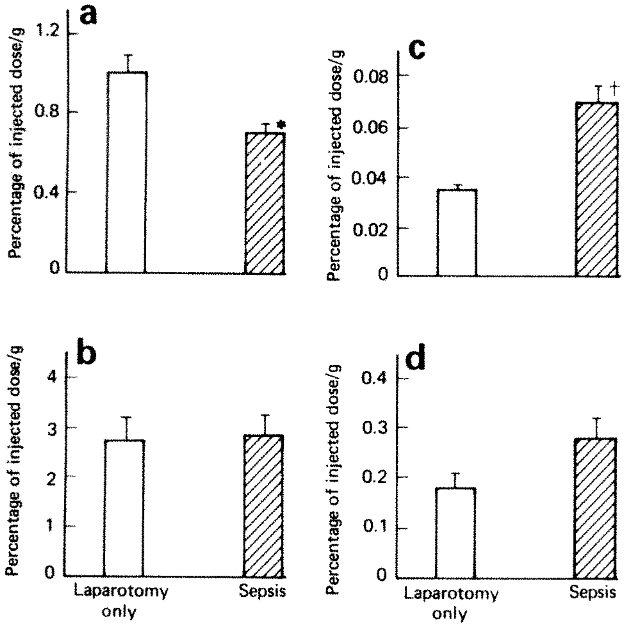

Figure 5 *Organ distribution of low dose technetium tin colloid in* **a** *liver,* **b** *spleen,* **c** *bone and* **d** *lung.* * $P<0{\cdot}05$, † $P<0{\cdot}01$ (*laparotomy only* versus *sepsis, Mann–Whitney* U *test*

this has been shown to correlate with the blood clearance and liver uptake of gelatinized RE test lipid emulsion. Similarly, low plasma fibronectin concentrations have been found after elective operations in patients[11–13]. In these studies, fibronectin returned to preoperative values within 3–7 days.

The reasons for the reduction of plasma fibronectin shortly after injury may be: consumption of opsonin in the RE clearance of particulate material (collagenous debris and possibly bacteria) which enter the circulation after being produced by tissue injury; incorporation into fibrin clots[14]; a reduction in synthesis; or deposition in the healing wound[15–17]. Opsonic consumption and wound deposition are the most likely causes. Radiolabelled fibronectin has been shown to disappear rapidly from the circulation and to be deposited within 15 min of injection in the injured tissues of a rat trauma model[16]. Studies of critically ill surgical patients have reported a significantly greater reduction in fibronectin in patients with septic complications[18]. The reduction in plasma fibronectin concentrations in this study was similar for the sepsis and laparotomy only groups but occurred earlier in the septic animals which may reflect greater opsonic consumption or wound deposition of fibronectin.

The transient reduction in fibronectin was followed by a significant increase in its concentration in both groups. The peak level of plasma fibronectin was not only significantly greater in the septic animals but also occurred later than the peak level in the laparotomy only group. One other study has measured the temporal response of fibronectin over a 2-week period in rats made septic by the intraperitoneal placement of opened ileum taken from another animal[4]. These workers also found that the increase in fibronectin occurred later than in the control group. This difference may be due to greater consumption of fibronectin in the septic animal.

Restoration of fibronectin levels in the post-injury period has been correlated with recovery of RE function[19]. The increase in plasma fibronectin above pre-injury levels may serve to augment local defence as well as the RE clearance of circulating bacteria and products of sepsis or tissue injury. This hypothesis may be valid for animals that undergo laparotomy only but the elevation of plasma fibronectin in animal models of sepsis has been shown to be associated with persistent impairment of RE function[3,5]. Lanser and Saba suggested that the increase in fibronectin may precede the recovery of RE phagocytic function[20] but, as this study has shown, RE functional depression is still present at 2 weeks. Grossman *et al.* found that fibronectin values in septic rats returned to normal by the end of the first week but remained elevated in non-surviving animals until death[4]. Therefore, in animal models of sepsis there seems to be an inverse relationship between fibronectin levels and RE function that contrasts with septic surgical patients in whom low levels correlate with impaired RE function.

The return to normal values of plasma fibronectin by the end of the first week may have coincided with the septic, necrotic focus being 'walled off' and thereby reducing the amount of collagenous debris and bacteria reaching the liver and systemic circulation. Further fluctuations in fibronectin concentrations may be related to the healing process. Fibronectin is important for initiating repair[21] and is a major component present in mature granulation tissue at 14 days after injury[17]. The role of fibronectin in local defence might be to augment phagocytosis by neutrophils and peritoneal macrophages to aid the clearance of fibrin, tissue debris and bacteria and thus inhibit their systemic absorption[20]. Delayed absorption of bacteria or exotoxin may aid immediate survival while inefficient absorption may lead to abscess formation and a greater long-term mortality rate.

It is concluded that the RE failure found in septic animals is due to intrinsic Kupffer cell dysfunction. This depression of RE function results in delayed RE dependent blood clearance and increased uptake of particulate matter by other RE cells such as the bone marrow macrophages. The reason for the biphasic response of plasma fibronectin to sepsis is not known but several factors may be important. These factors include consumption of plasma fibronectin and increased release or synthesis of the protein. Further work is needed to establish the mechanisms of RE cellular failure and fibronectin changes during sepsis.

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Effect of nutritional status on acute phase protein response to elective surgery

A. M. Cruickshank, D. T. Hansell†, H. J. G. Burns† and A. Shenkin

Department of Biochemistry and †Department of Surgery, Royal Infirmary, Glasgow, G4 0SF, UK

Correspondence to:
Dr A. M. Cruickshank

The aim of this study was to assess the effect of nutritional status on the acute phase protein response to elective surgery. Matched pairs of patients with gastric or colorectal cancer were studied. Undernourished patients (body-weight <80 per cent of ideal and triceps skinfold thickness <65 per cent of standard) were matched with controls (body-weight >95 per cent of ideal and *triceps skinfold thickness >80 per cent of standard) for age, sex, type of pathology and surgery. Blood samples taken preoperatively and on days 1–5 after operation were analysed for C-reactive protein, α_1-antitrypsin, α_1-acid glycoprotein, albumin, prealbumin and transferrin. There was no significant difference in any of the preoperative protein concentrations between the two groups although undernourished patients tended to have lower transferrin concentrations (mean ± s.e.m., 2·2 ± 0·3 g/l) than the control group (2·9 ± 0·1 g/l). C-reactive protein response was significantly smaller in the undernourished group than in the control group* (P = 0·05, *Mann–Whitney* U *test). The responses of the other acute phase proteins did not differ between the two groups. There was no difference in the length of hospital stay after operation when undernourished patients (mean ± s.e.m., 17·7 ± 3·0 days) were compared with controls (14·3 ± 3·6 days). Undernourished patients therefore have an attenuated C-reactive protein response to elective surgery. The significance of this in relation to morbidity and mortality in severely ill patients requires further investigation.*

Keywords: Acute phase proteins, C-reactive protein, nutritional status

Following tissue injury in humans, a variety of physiological and biochemical responses have been described[1]. Of particular interest is the significant alteration that occurs in the serum concentrations of certain proteins[2,3]. These proteins are collectively known as acute phase proteins (APPs) and most of them are synthesized by the liver. After trauma the plasma levels of these proteins may increase (positive APPs) or decrease (negative APPs). Although many aspects of this protein response remain unclear and our understanding of the functions and biological significance of these proteins is limited, it is generally assumed that they perform a protective role by limiting tissue damage and promoting repair and healing[4]. It is possible therefore that any condition which impairs the APP response (APPR) may limit ability to survive injury.

Few studies have examined the relationship between nutritional status and APPR in humans. If poor nutritional status resulted in impairment of the APPR, then the apparent relationship between malnutrition and increased postoperative morbidity[5,6] might, in part, be explained. The object of the present study was to determine the effect of undernutrition on the ability of patients to mount an APPR to elective surgery.

Patients and methods

Twelve patients undergoing elective resection of either gastric or colorectal cancer were identified for study. Preoperative nutritional status was assessed using anthropometry. Patients were considered to be undernourished if body-weight was <80 per cent of ideal[7] and triceps skinfold thickness was <65 per cent of the standard[8]. Patients with clinical evidence of oedema were excluded. Undernourished patients were matched with normally nourished controls whose body-weight was >95 per cent of ideal and triceps skinfold thickness was >80 per cent of standard. These patients were matched for age, sex, pathology and surgery. Patients were excluded if any complications occurred at operation or within the period under study. Six pairs completed the study (two female, four male; two gastric, four colorectal carcinoma; *Table 1*). Venous blood samples were taken preoperatively and on days 1–5 after surgery.

Each blood sample was analysed for: C-reactive protein, (TDX system, Abbott Diagnostics Inc, North Chicago, Illinois, USA); α_1-antitrypsin, α_1-acid glycoprotein and transferrin (antisera and standard from Atlantic Antibodies, Scarborough, Maine, USA using the Encore Chemistry System, Baker Instruments, Windsor, Berkshire, UK); prealbumin (reagents from Serotec, Bicester, Oxon, UK); and albumin (by the bromocresol green method on a Hitachi 704, BCL, Lewes, East Sussex, UK).

The APPR after surgery in the undernourished group was compared with the response in the matched control group. Statistical analysis of results was carried out using a paired Student's *t* test and Mann–Whitney *U* test.

Results

There was no difference in the length of postoperative hospital stay between undernourished patients (mean ± s.e.m., 17·7 ± 3·0 days) and controls (14·3 ± 3·6 days).

Preoperatively there was no significant difference in protein

Table 1 *Patient characteristics of undernourished and matched control groups*

	Control group	Undernourished group
Age (years)	67 ± 5·0	67 ± 3·8
Percentage of ideal body-weight	115 ± 5·4	76 ± 1·7
Percentage weight loss	12 ± 2·3	19 ± 2·7*
Percentage of standard arm muscle circumference	99 ± 2·5	84 ± 2·3*
Percentage of standard triceps skinfold thickness	115 ± 16·9	43 ± 4·1

Values are mean ± s.e.m., $n = 6$; * $P < 0·2$ (paired *t* test, control *versus* undernourished)

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Table 2 *Preoperative concentrations of acute phase proteins in undernourished patients and controls*

	Control group	Undernourished group
α_1-Antitrypsin (g/l)	2·4±0·2	2·5±0·3
α_1-Acid glycoprotein (g/l)	1·3±0·1	1·1±0·1
C-reactive protein (mg/l)	29±5·9	25±6·5
Transferrin (g/l)	2·9±0·1	2·2±0·3
Prealbumin (mg/l)	221±26·4	208±23·1
Albumin (g/l)	36±1·9	37±1·1

Values are mean ±s.e.m.

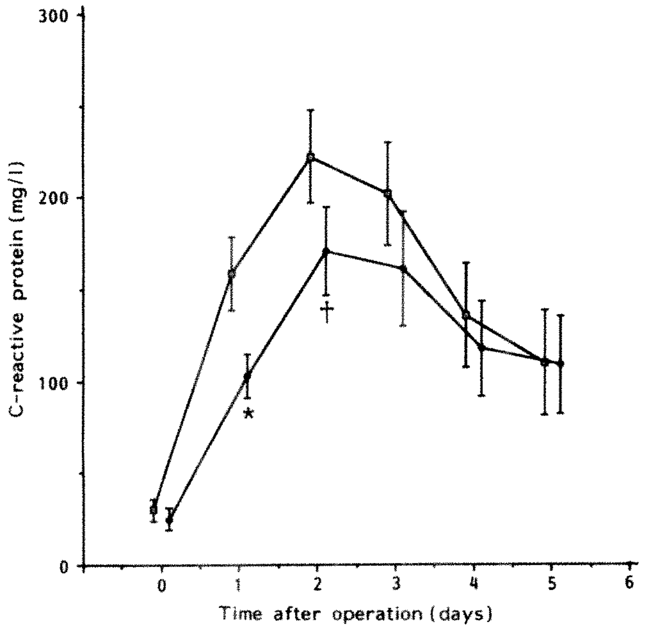

Figure 1 *Serum C-reactive protein response to elective surgery. Day 0 represents preoperation value;* ●, *undernourished group;* ☐, *control group. Values are mean ±s.e.m.* * $P<0{\cdot}05$, † $P<0{\cdot}02$ *(undernourished* versus *control)*

concentrations between the two groups, although undernourished patients tended to have lower transferrin concentrations (*Table 2*).

Serum levels of C-reactive protein rose in both groups after surgery. Maximum levels were reached after approximately 48 h and were significantly lower in the undernourished group (mean±s.e.m., 171·0±23·6 mg/l) than in the control group (221·5±24·6 mg/l; $P<0{\cdot}02$, paired *t* test; *Figure 1*). Moreover the total response to C-reactive protein (area under curve) was significantly lower in undernourished patients (mean±s.e.m., 4728±749) than in the controls (6395±681; $P<0{\cdot}05$, paired *t* test). The significance of this observation was confirmed by nonparametric unpaired statistical analysis (control median, 6884; undernourished median, 4915; $P=0{\cdot}05$, Mann–Whitney *U* test).

In both groups α_1-antitrypsin and α_1-acid glycoprotein levels rose significantly ($P<0{\cdot}001$ and $P<0{\cdot}01$ respectively, paired *t* test) to reach a maximum at approximately 4 days after operation (*Figures 2* and *3*). There was no difference between the two groups in the responses of either of these proteins.

The responses of the negative APPs, namely albumin, prealbumin and transferrin, did not differ between the two groups (*Table 3*).

Discussion

Undernourished patients had an attenuated C-reactive protein response whereas the response of the other APPs (negative and positive) did not differ between the undernourished group and controls. The increase in serum concentration of the APPs following injury is primarily as a result of increased hepatic synthesis, although there is evidence to suggest that α_1-acid glycoprotein is produced by other cells[9]. C-reactive protein is synthesized exclusively by hepatocytes, and tissue injury results in the progressive recruitment of increasing numbers of hepatocytes to synthesis[10]. In our patients, the magnitude and rate of increase of C-reactive protein concentration were approximately tenfold greater than those of α_1-antitrypsin and α_1-acid glycoprotein concentrations, and thus hepatic synthesis of C-reactive protein may be more sensitive to lack of substrate than is the synthesis of other APPs. Muscle breakdown is thought to

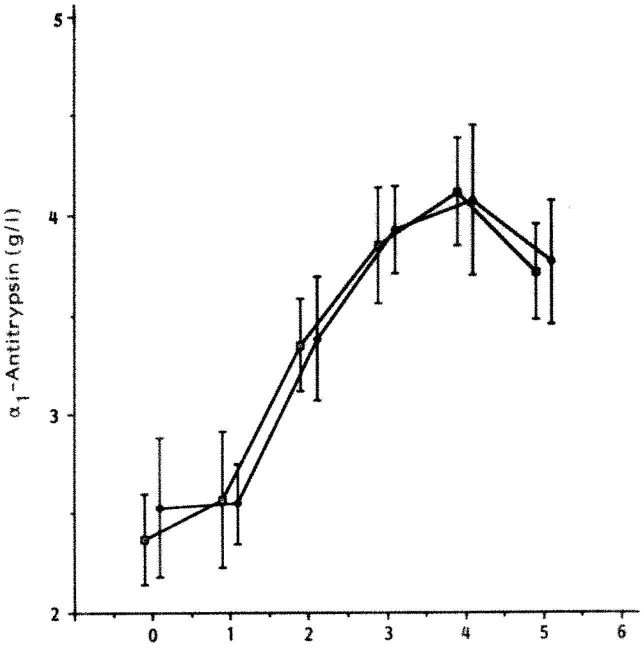

Figure 2 *Serum α_1-antitrypsin response to elective surgery. Day 0 represents preoperation value;* ●, *undernourished group;* ☐, *control group. Values are mean ±s.e.m.*

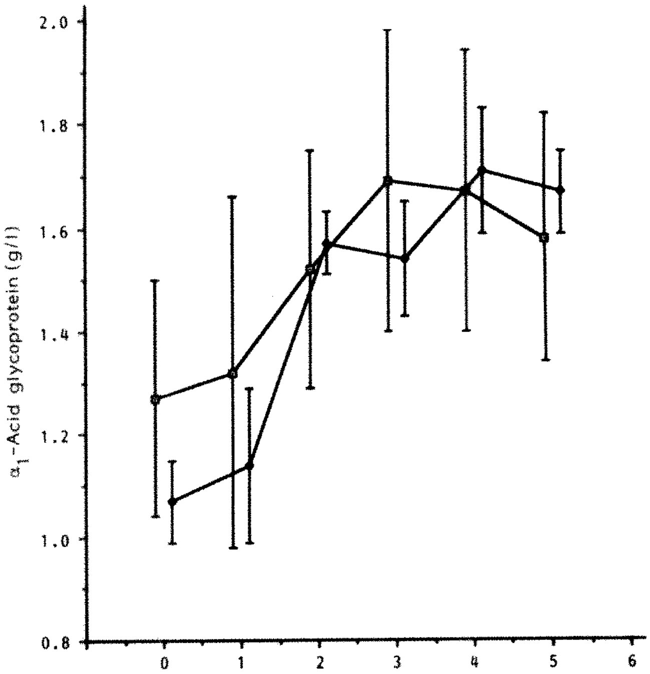

Figure 3 *Serum α_1-acid glycoprotein response to elective surgery. Day 0 represents preoperation value;* ●, *undernourished group;* ☐, *control group. Values are mean ±s.e.m.*

Table 3 *Response to surgery of negative acute phase proteins*

	Control group						Undernourished group					
	Pre-operative	Postoperative day					Pre-operative	Postoperative day				
		1	2	3	4	5		1	2	3	4	5
Albumin (g/l)	36±2	33±1	31±1	32±1	31±2	30±2	37±1	34±2	31±1	32±2	32±1	30±1
Prealbumin (mg/l)	221±26	162±28	135±20	121±23	104±18	140±20	208±23	163±17	142±12	152±21	130±19	97±15
Transferrin (g/l)	2·9±0·1	2·2±0·3	1·9±0·2	1·9±0·3	1·8±0·1	1·7±0·1	2·2±0·3	1·9±0·5	1·8±0·4	1·6±0·2	1·5±0·2	1·5±0·2

Values are mean ±s.e.m., $n=6$

be related to the acute phase response[11,12]. Thus depleted skeletal muscle protein stores (as reflected by decreased arm muscle circumference, *Table 1*) may cause impaired substrate supply to the liver and directly affect the liver acute phase reactant synthetic capacity[13].

Our results differ from those of Dominioni *et al.*[14] who looked at the APPR to gastrectomy in 'undernourished' patients and controls with gastric cancer and found that α_1-acid glycoprotein was the only APP affected by malnutrition, the peak concentration being lower in the 'undernourished' group. However, in that study the sole criterion for classifying a patient as undernourished was a serum albumin concentration <32 g/l. Another study which examined the relationship between nutritional status and acute phase mediators, and which suggested that patients with mild to moderate malnutrition had an intact ability to produce leucocyte endogenous mediator after elective surgery, also used serum albumin concentrations as a marker of nutritional status[15]. It is now generally accepted that such use of serum albumin concentration is invalid. The form of undernutrition most often present in hospital patients in the developed world is moderate protein-calorie malnutrition which is poorly reflected by serum albumin concentration[16]. Serum albumin concentration is more dependent on its distribution between intravascular and extravascular fluid compartments and on hydration state than on any change in its synthetic or catabolic rate[17]. We chose to use anthropometric criteria to diagnose protein-calorie malnutrition. Our finding of similar preoperative albumin concentrations in the undernourished and control groups confirms that serum albumin concentration is a poor marker for protein-calorie malnutrition.

The acute phase response is brought about by a variety of as yet incompletely characterized regulatory mediators which include interleukin 1[18], and cachectin[19]. More recently interleukin 6 (originally described as interferon B_2) has also been shown to be an important mediator of the APPR and to be identical to hepatocyte stimulating factor 1[20]. In addition to affecting hepatic protein synthesis directly it is likely that undernutrition affects these mediating factors, a premise supported by recent work in protein-depleted guinea-pigs[21]. Bauman *et al.*[19] have shown that in rat hepatoma cells distinct sets of acute phase plasma proteins are stimulated by separate human hepatocyte stimulating factors (HSFI and HSFII) and with a different sensitivity relative to interleukin 1 and cachetin stimulation. If some of these factors are more sensitive to undernutrition than others, this could partly explain why undernourished patients in our study showed normal responses of some APPs but impaired response of C-reactive protein.

In this study, the attenuated C-reactive protein response of the undernourished group was not associated with any difference in outcome in terms of length of postoperative hospital stay. Patients who developed complications were specifically excluded from our study to eliminate any factors that might affect APP levels. One may postulate that had sepsis occurred, then patients with an impaired C-reactive protein response may have had a poorer prognosis. Indeed an association between an impaired APPR in severely septic surgical patients and poor outcome has been demonstrated[22]. Although the precise function of C-reactive protein is not known, it is likely to be beneficial because of the stable evolutionary conservation of this protein. Human C-reactive protein is an effective precipitin and agglutinin of soluble and particulate ligands, and is probably involved in activation of the classical complement pathway[23].

In summary, we found that undernourished patients had an attenuated C-reactive protein response to elective surgery although the responses of other APPs were unaffected. We conclude that undernutrition does affect aspects of the APPR in humans. The clinical significance of this finding remains to be determined.

Acknowledgements

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Case report

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Appendicitis complicating meconium ileus equivalent

J. A. P. Rimmer, J. M. Gilbert and T. G. Allen-Mersh

Academic Surgical Unit, St. Stephen's Hospital, Chelsea, London SW10 9TH, UK
Correspondence to: Mr J. A. P. Rimmer

Adults with cystic fibrosis are susceptible to partial or complete bowel obstruction induced by abnormally viscid mucofaecal material in the terminal ileum and caecum. This condition, which has been termed 'meconium ileus equivalent'[1], is often associated with cessation of pancreatic enzyme replacement or upper respiratory infection[2]. Complications of meconium ileus equivalent include intussusception and volvulus[1]. We report a case of an adult with cystic fibrosis in whom appendicitis was associated with obstruction of the appendix lumen by abnormally viscid mucofaecal material.

Case report

A 24-year-old man with cystic fibrosis, which had been diagnosed at 1 year of age, presented with a 1 month history of recurrent central and lower abdominal pain. The onset of pain coincided with changing from Pancrex V (Paines and Byrne Ltd., UK) to 'Creon' (Duphar Laboratories Ltd., UK) oral pancreatic enzyme supplement, which had also resulted in constipation. Three days before admission the pain became more severe, and localized to the right iliac fossa. The clinical features of fever, central abdominal pain shifting to the right iliac fossa followed by guarding and rebound tenderness, and the presence of a leucocytosis suggested appendicitis, but could also have been the result of meconium ileus equivalent syndrome[1]. At operation an acutely inflamed, distended appendix was removed and the patient made an uneventful recovery. The appendix measured 2 cm in diameter and 7·5 cm in length, and the lumen was filled with abnormally viscid mucofaecal material. Histological examination showed features of acute suppurative appendicitis and confirmed that the lumen was distended with mucofaecal material (*Figure 1*).

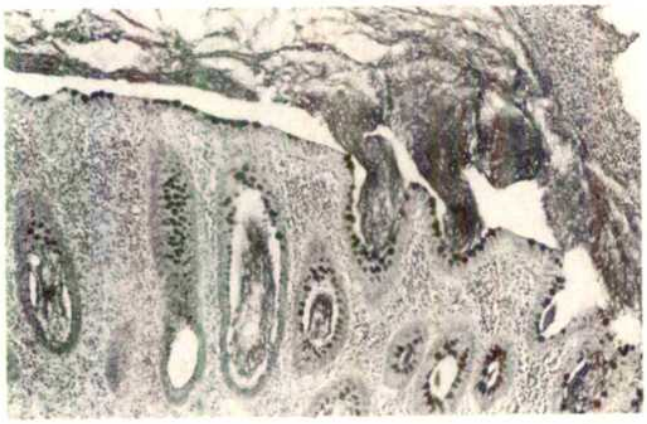

Figure 1 *Photomicrograph of a cross-section of the appendix showing acute inflammation and distension by mucofaecal material (periodic acid–Schiff, magnification ×8)*

Discussion

Acute appendicitis is thought to develop in 0·5–1·6 per cent of patients with cystic fibrosis[2–4]. The diagnosis is usually made late and is associated with a high incidence of abdominal and pelvic sepsis, resulting in a mortality rate of up to 33 per cent[3]. It has been suggested that the lower incidence of appendicitis in association with cystic fibrosis, compared with that in the general population (7 per cent)[3] may be the result of intraluminal mucofaecal material protecting the appendix from inflammation. However, this difference could be explained by the tendency to late diagnosis of appendicitis in patients with cystic fibrosis[3] resulting in spontaneous resolution without diagnosis in some less severe cases, and also by the difference in life expectancy between cystic fibrosis patients and the general population.

In our patient the lumen was filled with putty-like mucofaecal material and the appendix was inflamed. There was no evidence of a faecalith, worm, food debris, congenital band or any of the other known causes of acute appendicitis[5]. This, and the recent alteration in bowel habit produced by the change in enzyme supplement, suggests that the mucofaecal material contributed to the development of appendicitis. Thus appendicitis appears to have been a complication of meconium ileus equivalent.

Abdominal pain is a common complaint in patients with cystic fibrosis and, in addition to meconium ileus equivalent, may be a consequence of malabsorption, acute pancreatitis, gallstones, or peptic ulceration[6]. Thus, diagnosis of the acute abdomen in cystic fibrosis can be difficult and may lead to late diagnosis of appendicitis[3].

With increased life expectancy[1,7], appendicitis can be expected to occur more frequently in patients with cystic fibrosis. The dogma that appendicitis in cystic fibrosis is rare may be dangerous. At best the evidence for this is not conclusive and such a view may encourage a tendency to late diagnosis and increased morbidity in these patients.

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Anergy in patients with biliary lithiasis

A prospective study was carried out in 428 subjects (212 controls and 216 patients) to evaluate the delayed cell-mediated immune response preoperatively in patients with biliary lithiasis. The delayed hypersensitivity response was assessed by a Multitest and subjects were classified as immunocompetent, relatively anergic or anergic. Significant differences were found between control subjects and patients with cholelithiasis compared with those with acute cholecystitis ($P<0{\cdot}01$), *non-icteric choledocholithiasis* ($P<0{\cdot}01$) *and choledocholithiasis with jaundice* ($P<0{\cdot}05$). *There were also differences between patients with icteric and non-icteric choledocholithiasis* ($P<0{\cdot}02$). *Seven possible causative factors for anergy were evaluated: a haemoglobin concentration of* $\leqslant 12$ *g/l and a haematocrit of* $\leqslant 35$ *per cent were related to the appearance of anergy and relative anergy in patients with acute cholecystitis. Bilirubin levels* $\geqslant 34$ *μmol/l were found in 60 per cent of patients with choledocholithiasis and relative anergy and in 80 per cent of those who were anergic* ($P<0{\cdot}001$). *These results show a high incidence of failure of the cell-mediated immune response in patients with acute cholecystitis (71 per cent) and icteric choledocholithiasis (82 per cent). In the latter, jaundice appears to be associated with this failure. A close correlation between relatively anergic and anergic state and the development of postoperative septic complications was found.*

Keywords: Anergy, delayed cell-mediated immune response, biliary lithiasis, jaundice

M. Caínzos, J. Potel and J. L. Puente

Service of General Surgery,
Hospital General de Galicia,
C/Galeras s.n, Santiago de
Compostela, Spain
Correspondence to.
Professor M. Caínzos,
Departamento de Cirugia, Hospital
de Galicia, C/ Galeras s n.,
Santiago de Compostela, Spain

The rates of postoperative infection secondary to surgery performed to treat biliary lithiasis depend on the site of the gallstone(s) in the biliary tract. Thus, while in uncomplicated cholelithiasis postoperative infections are rare, their incidence increases considerably if a stone becomes impacted at the gallbladder's outlet, producing acute cholecystitis, or if it has migrated to and obstructed the common bile duct.

Anergy has been established in several studies[1–7] as a risk factor for the development of postoperative infection. Therefore, we have evaluated preoperatively the status of the delayed cell-mediated immune response in patients with lithiasis of the common or accessory biliary ducts.

Patients and methods

A 3-year (1984–86) prospective study was undertaken in 428 subjects, 212 controls and 216 patients, with biliary lithiasis with a view to analysing the cell-mediated immune response The control group consisted of 110 men (51·9 per cent) and 102 women (48·1 per cent). All were in good general health, had no history of recent weight loss and none was on medication. Ages ranged from 21 to 82 years (mean age ± s.d 44·2 ± 14 9 years)

The patient group was composed of 216 subjects with biliary lithiasis and comprised 135 with uncomplicated cholelithiasis, 38 with acute cholecystitis, 21 with non-icteric choledocholithiasis and 22 with icteric choledocholithiasis. The preoperative diagnosis of gallstones and acute cholecystitis was made by history and physical examination, leucocyte count, plain X-ray film of the abdomen and ultrasonography (with or without additional intravenous cholangiography) There were 63 men (29·2 per cent) and 153 women (70·8 per cent), ranging in age from 14 to 91 years (mean age ± s.d. 52·4 ± 16·3 years) None had received radiation therapy or chemotherapy or had undergone other surgery during the 3 months preceding surgery.

The Multitest* technique was used to evaluate the delayed cell-mediated immune response. This method of instant multipuncture involves injection of seven antigens and one glycerin control. The antigens were each given in a dose of 0 03 ml and consisted of tetanus, 550 000 Merieux units/ml; diphtheria, 1 100 000 Merieux units/ml; *Streptococcus* (group C), 2000 Merieux units/ml, tuberculin, 300 000 units/ml; *Candida*, 2000 Merieux units/ml; *Trichophyton*, 150 Merieux units/ml; and *Proteus mirabilis*, 150 Merieux units/ml. The control was a 70 per cent weight/volume solution of glycerol.

Antigens were injected in the volar surface of the forearm and results were read at 48 h. The response was considered positive when the mean of the greater and lesser diameters was >2 mm. The sum of the mean response to the seven antigens constituted each patient's 'score'. There were three groups of responses· immunocompetent, with a score >10 mm in men and >5 mm in women, relative anergy, with a score of 2–10 mm in men and 2–5 mm in women; and anergy, with a negative response or a score <2 mm. All patients were hospitalized for 2 days after antigen administration, and the delayed hypersensitivity test was performed on all patients preoperatively

The patients were monitored daily for clinical signs of a major septic complication during the postoperative period and on an outpatient basis at 4 weeks after discharge. Major sepsis was defined as intra-abdominal abscess, bacteraemia, lung infection, anastomotic fistula, septic shock, and death attributed to septic causes

Seven possible causative factors for anergy were studied age $\geqslant 60$ years; serum albumin $\leqslant 30$ g/l, leucocyte count $\geqslant 9000/\text{mm}^3$, haemoglobin $\leqslant 12$ g/l, haematocrit $\leqslant 35$ per cent, total bilirubin $\geqslant 34$ μmol/l, and presence of cirrhosis To this end, blood was drawn from all patients for analysis at the time of antigen administration.

In those patients in whom the gross appearance of the liver during surgery was suggestive of cirrhosis, a biopsy was taken for subsequent histological analysis

Statistical analysis was performed by means of the χ^2 test with the Yates' correction. Values of $P<0{\cdot}05$ were considered significant

Results

Delayed hypersensitivity response

No differences were seen in the delayed hypersensitivity response between controls and patients with uncomplicated cholelithiasis (*Table 1*). In the case of relative anergy there was a statistically significant difference between patients with uncomplicated cholelithiasis and those with acute cholecystitis ($P<0{\cdot}01$) and icteric choledocholithiasis ($P<0{\cdot}05$) Similarly, with regard to the anergy response, there was a significant difference between uncomplicated cholelithiasis and acute cholecystitis ($P<0{\cdot}001$) and non-icteric and icteric choledocholithiasis ($P<0{\cdot}01$ and $P<0{\cdot}001$ respectively). A pronounced difference was found between patients with non-icteric choledocholithiasis and those with jaundice ($P<0{\cdot}02$). When the anergic and relatively anergic patients were combined there

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* *Multitest CMI Merieux Institute, Miami, Florida, USA*

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was a statistically significant difference between patients with uncomplicated cholelithiasis and those with acute cholecystitis ($P<0\cdot001$), uncomplicated cholelithiasis and non-icteric choledocholithiasis ($P<0\cdot01$), uncomplicated cholelithiasis and icteric choledocholithiasis ($P<0\cdot001$), and non-icteric and icteric choledocholithiasis ($P<0\cdot01$).

The patients with the greatest alteration of the delayed cellular immune response were those with choledocholithiasis and jaundice, as 82 per cent of the 22 patients in this group were either anergic or relatively anergic.

Anergy: risk factors

Of the seven risk factors for anergy, three had no statistical relationship with its development, namely age ≥60 years (*Table 2*), serum albumin ≤30 g/l (*Table 3*), or leucocyte count ≥9000/mm^3 (*Table 4*).

In patients with acute cholecystitis, haemoglobin values of ≤12 g/l were related to relative anergy ($P<0\cdot01$) or anergy ($P<0\cdot05$; *Table 5*). In these same patients, relative anergy was significantly associated with a haematocrit of ≤35 per cent ($P<0\cdot01$; *Table 6*).

Table 1 *Response of delayed hypersensitivity in controls and patients with gallstones*

	Immunocompetent	Relatively anergic	Anergic	Relatively anergic + anergic
Control group ($n=212$)	174 (82·1)	28 (13·2)	10 (4·7)	38 (17·9)
Cholelithiasis ($n=135$)	117 (86·7)	12 (8·9)	6 (4·4)	18 (13·3)
Acute cholecystitis ($n=38$)	11 (29)	11 (29)	16 (42)	27 (71)
Choledocholithiasis				
Non-icteric ($n=21$)	13 (62)	4 (19)	4 (19)	8 (38)
Icteric ($n=22$)	4 (18)	6 (27)	12 (54)	18 (82)

Values in parentheses are percentages

Table 2 *Relationship between age and delayed hypersensitivity response*

	Immunocompetent	Relatively anergic	Anergic	Relatively anergic + anergic
Cholelithiasis ($n=135$)	24/117 (20·5)	5/12 (42)	2/6 (33)	7/18 (39)
Acute cholecystitis ($n=38$)	8/11 (73)	8/11 (73)	9/16 (56)	17/27 (63)
Choledocholithiasis				
Non-icteric ($n=21$)	4/13 (31)	3/4 (75)	2/4 (50)	5/8 (62)
Icteric ($n=22$)	3/4 (75)	5/6 (83)	9/12 (75)	14/18 (78)

Values are number of patients ≥60 years old over the total number of patients in each category. Values in parentheses are percentages

Table 3 *Relationship between serum albumin and delayed hypersensitivity response*

	Immunocompetent	Relatively anergic	Anergic	Relatively anergic + anergic
Cholelithiasis ($n=135$)	3/117 (2·6)	1/12 (8)	1/6 (17)	2/18 (11)
Acute cholecystitis ($n=38$)	3/11 (27)	3/11 (27)	5/16 (31)	8/27 (30)
Choledocholithiasis				
Non-icteric ($n=21$)	1/13 (8)	1/4 (25)	0/4	1/8 (12)
Icteric ($n=22$)	2/4 (50)	4/6 (67)	7/12 (58)	11/18 (61)

Values are number of patients with serum albumin levels ≤30 g/l over the total number of patients in each category. Values in parentheses are percentages

Table 4 *Relationship between leucocyte count and delayed hypersensitivity response*

	Immunocompetent	Relatively anergic	Anergic	Relatively anergic + anergic
Acute cholecystitis ($n=38$)	3/11 (27)	2/11 (18)	7/16 (44)	9/27 (33)
Choledocholithiasis				
Non-icteric ($n=21$)	1/13 (8)	2/4 (50)	0/4	2/8 (25)
Icteric ($n=22$)	0/4	1/6 (17)	5/12 (42)	6/18 (33)

Values are number of patients with leucocyte counts ≥9000/mm^3 over the total number of patients in each category. Values in parentheses are percentages

Table 5 *Relationship between haemoglobin concentration and delayed hypersensitivity response*

	Immunocompetent	Relatively anergic	Anergic	Relatively anergic + anergic
Cholelithiasis ($n=135$)	8/117 (6·8)	1/12 (8)	0/6	1/18 (6)
Acute cholecystitis ($n=38$)	0/11	6/11 (54)*	4/16 (25)†	10/27 (37)‡
Choledocholithiasis				
Non-icteric ($n=21$)	2/13 (15)	1/4 (25)	0/4	1/8 (12)
Icteric ($n=22$)	2/4 (50)	0/6	5/12 (42)	5/18 (28)

Values are number of patients with haemoglobin concentrations ≤12 g/l over the total number of patients in each category. Values in parentheses are percentages. * $P<0\cdot01$, $\chi^2=8\cdot24$, *versus* immunocompetent, † $P<0\cdot05$, $\chi^2=5\cdot08$, *versus* immunocompetent; ‡ $P<0\cdot02$, $\chi^2=5\cdot85$, *versus* immunocompetent

Table 6 *Relationship between haematocrit and delayed hypersensitivity response*

	Immunocompetent	Relatively anergic	Anergic	Relatively anergic + anergic
Cholelithiasis ($n=135$)	7/117 (6·0)	2/12 (17)	0/6	2/18 (11)
Acute cholecystitis ($n=38$)	2/11 (18)	6/11 (54)*	2/16 (12)	8/27 (30)
Choledocholithiasis				
Non-icteric ($n=21$)	1/13 (8)	0/4	0/4	0/8
Icteric ($n=22$)	2/4 (50)	0/6	3/12 (25)	3/18 (17)

Values are number of patients with a haematocrit ⩽35 per cent over the total number of patients in each category. Values in parentheses are percentages. * $P<0\cdot01$, $\chi^2=8\cdot24$, *versus* immunocompetent

Table 7 *Relationship between serum bilirubin concentration and delayed hypersensitivity response*

	Immunocompetent	Relatively anergic	Anergic	Relatively anergic + anergic
Cholelithiasis ($n=135$)	2/117 (1·7)	1/12 (8)	1/6 (17)	2/18 (11)
Acute cholecystitis ($n=38$)	2/11 (18)	2/11 (18)	3/16 (19)	5/27 (18)
Choledocholithiasis ($n=43$)	5/17 (29)	6/10 (60)	13/16 (81)*	19/26 (73)†

Values are number of patients with serum bilirubin concentration ⩾34 μmol/l over the total number of patients in each category. Values in parentheses are percentages * $P<0\cdot01$, $\chi^2=7\cdot82$, *versus* immunocompetent; † $P<0\cdot02$, $\chi^2=6\cdot28$, *versus* immunocompetent

Regarding jaundice, of those patients with choledocholithiasis, 60 per cent of those with relative anergy and 81 per cent ($P<0\cdot01$) of those with anergy had bilirubin values ⩾34 μmol/l (*Table 7*).

In three patients, cirrhosis was histologically confirmed. One had uncomplicated cholelithiasis, another had non-icteric choledocholithiasis and a third had icteric choledocholithiasis. Though all three were anergic, this was too low an incidence of cirrhosis to permit valid statistical conclusions to be drawn.

Relationship between anergy and postoperative sepsis

Of the 216 patients studied, 198 underwent surgery. Of these, 138 were immunocompetent, 28 showed relative anergy and 32 were anergic. Of the 138 immunocompetent patients only two (1·4 per cent) developed major septic complications in the postoperative period (one bacteraemia and one right subphrenic abscess). Of the 28 patients with relative anergy, four (14 per cent) had major septic complications (three bacteraemia and one right subphrenic abscess). Similarly, of the 32 anergic patients, five (16 per cent) had postoperative sepsis (two bacteraemia and three septic shock and death (anergic *versus* immunocompetent patients, $\chi^2=19\cdot29$, $P<0\cdot001$; relatively anergic *versus* immunocompetent patients, $\chi^2=11\cdot9$, $P<0\cdot001$). Of the nine relatively anergic and anergic patients who developed postoperative septic complications, eight were jaundiced.

Discussion

Anergy, defined as a failure of the delayed cell-mediated immune response, has been emphasized in several studies[1–7] as a factor in the development of postoperative sepsis. We have also confirmed this as a risk factor for postoperative sepsis in a study of 503 patients[8] and showed a close correlation between the presence of preoperative anergy or relative anergy and the development of postoperative infection. Since biliary lithiasis is one of the most common problems encountered in surgery, we investigated delayed cellular immunity status preoperatively in patients with lithiasis of the common and accessory bile ducts.

The results of the present study stress that patients with uncomplicated cholelithiasis have only a slight risk of developing anergy, the risk being the same as that of healthy controls. In patients with stones that migrate to but do not obstruct the common bile duct, the risk increases, but the greatest risk is found in patients with acute cholecystitis and especially in those with obstructive choledocholithiasis; 71 and 82 per cent respectively of these groups of patients are anergic or relatively anergic. This fact could explain the high rate of infection in patients with acute cholecystitis and in those with obstructive choledocholithiais. Stone *et al.*[9] established that the rate of surgical infection in chronic cholecystitis was 8·9 per cent as opposed to 17 per cent in acute cholecystitis. Hollands *et al.*[10] found a surgical wound infection rate of 8 per cent in patients with no obstruction of the gallbladder. The serious risk that infection poses has been pointed out by several authors[11–15] who noted that high infection rate increases surgical morbidity and mortality. The bacteriological aspects of these infections have been discussed in several studies[16–21].

With the relationship between anergy and acute cholecystitis on the one hand, and choledocholithiasis (and especially obstructed choledocholithiasis) on the other, the factors responsible for this anergy must be determined. In our study we have elected to analyse seven possible factors, namely advanced age[4,22,23], hypoalbuminaemia[24–27], leucocytosis[28], decreased haemoglobin concentration and haematocrit[29–31], cirrhosis[32], and hyperbilirubinaemia. We have demonstrated that neither advanced age, hypoalbuminaemia nor leucocytosis were responsible for anergy, although elsewhere[33] we did find a correlation between these parameters and anergy in other diseases. In the present series haemoglobin ⩽12 g/l and haematocrit ⩽35 per cent were related to the presence of anergy or relative anergy in patients with acute cholecystitis. Anergy was present in the three patients in whom cirrhosis was demonstrated, but the limited number of cases did not permit statistical conclusions to be drawn. However, a close association between an increase in serum bilirubin levels and the develoment of anergy or relative anergy was found in patients with choledocholithiasis; 60 per cent of the relatively anergic and 81 per cent of the anergic patients had a total bilirubin ⩾34 μmol/l. These rates of anergy are similar to those found by us in a previous study in which we examined the incidence of anergy in patients with jaundice due to various different disorders including tumours of the biliary tract and head of the pancreas[34].

Despite the fact that Brown *et al.*[35] and Ausobsky *et al.*[36] did not find any correlation between the presence of anergy and postoperative sepsis in surgical patients, an increasing number of authors are now reporting such a relationship. Our study confirms a close correlation between state of relative anergy and anergy and major postoperative sepsis. Although the rate of septic complications was similar in the relatively anergic and anergic groups, those of the anergic group were more serious, with three deaths due to sepsis compared with none of septic origin in either relatively anergic or immunocompetent patients.

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Pylorus-preserving pancreatectomy: functional results

D. R. Hunt and
R. McLean*

*University Department of Surgery, and *Department of Nuclear Medicine, The St. George Hospital, Kogarah, New South Wales 2217, Australia*

Correspondence to
Professor D. R. Hunt

The pylorus-preserving technique is reported as improving the functional results of pancreatectomy but it is complicated in the early postoperative period by delayed recovery of gastric function in a proportion of patients. We have examined early and late gastrointestinal function in a prospective study of 16 patients having this procedure. The late results appear better than reported results for conventional Whipple resection and the delay in early recovery does not appear to have any late sequelae, provided that it does not require gastric bypass for relief.

Keywords: Pancreatectomy, pylorus preservation, gastrointestinal function, gastric emptying

When Whipple *et al.*[1] reported in 1935 their first successful pancreaticoduodenectomy, the first part of the duodenum was transected and no portion of the stomach removed. However, in a paper published in 1945[2], Whipple described a modification of the original operation and this modification now bears his name. One of the changes from the original description was the addition of a 50 per cent gastrectomy. Although most current texts state that this is done to prevent ulceration, Whipple admitted that 'this was a mistake': the tumour was thought to be arising from the posterior wall of the antrum and only after the stomach was transected was the origin from the pancreas defined. In the following years, numerous techniques and modifications were described but it is worth noting that Kausch[3] and Watson[4] reported single cases where the pylorus was preserved and four of the 30 cases reported by Waugh and Clagett from the Mayo Clinic[5] had pyloric preservation. Notwithstanding, the Whipple technique became the standard curative procedure for carcinoma of the head of the pancreas and ampullary region for 35 years.

In 1978, Traverso and Longmire[6] reported two patients requiring pancreaticoduodenal resection in whom the stomach and pylorus were preserved and the duodenal bulb was anastomosed end-to-side to the jejunum. This operation has subsequently been referred to as the pylorus-preserving pancreatectomy. By 1986, Itani *et al.*[7] had collected details of 252 patients having this operation and concluded that the functional results were better with pylorus preservation than following the standard Whipple procedure where a portion of the stomach is removed. Warshaw and Torchiana[8] have highlighted problems with delayed gastric emptying and this delay occurred in 76 of the 252 patients collected by Itani[7]. Although the delay was usually transient, it persisted in a proportion of patients.

In assessing long-term function, preservation of the antropyloric segment appears to protect the patient from some of the nutritional and functional disabilities observed in those having the Whipple procedure. However, not all patients have experienced an entirely satisfactory course after pylorus-preserving pancreatectomy and it is not clear whether the late functional results were related to the initial delayed gastric emptying and apparent gastric malfunction.

Since 1980, 16 patients on the Gastrointestinal Surgical Unit at the St. George Hospital have had a pylorus-preserving pancreatectomy. This paper reports a prospective study of the functional results 3 months after operation and correlates them with the early recovery of gastric function.

Patients and methods

Clinical details of the 16 patients are summarized in *Table 1* The median age of the patients was 59·5 years (range 31–73). In nine patients, the indication for operation was periampullary carcinoma and all tumours were less than 3 cm in diameter; two patients had benign tumours causing common duct obstruction, five patients had resection for chronic pancreatitis. In 11 patients, only the head of the pancreas was resected. Total pancreatectomy was performed in five patients; three having had a tumour in combination with pre-existing diabetes and two patients having had chronic pancreatitis with small ducts and unremitting pain

At operation, the second, third and fourth parts of the duodenum were mobilized and resectability confirmed. The neurovascular attachments to the antrum and pylorus along the lesser curve and via the right gastric artery were carefully preserved. The gastroduodenal artery was divided close to its origin and this artery together with its associated lymph nodes and pancreaticoduodenal branches were removed with the specimen Continuity of the right gastroepiploic artery was therefore interrupted but the gastroepiploic arcade was preserved along the greater curvature. The duodenal bulb was transected 3 cm beyond the pylorus and, after completing the resection, the proximal jejunum was brought through a hole in the mesocolon and the divided first part of duodenum was anastomosed, end-to-side, to the jejunal loop, using

Table 1 *Clinical details for 16 patients having pylorus-preserving pancreatectomy*

Patient	Age (years)	Diagnosis	Date of operation	Resection	Outcome
1.	53	Chronic pancreatitis	17 04 80	Total	Alive
2.	68	Carcinoma	19 08 82	Total	Dead (10 days)
3.	58	Villous papilloma	11 11 82	Head	Alive
4.	64	Carcinoma	10 02 83	Total	Dead (12 months)
5	69	Carcinoma	22 09 83	Head	Dead (23 months)
6.	47	Chronic pancreatitis	15 03 84	Head	Alive
7.	51	Carcinoma	20 06 84	Head	Dead (6 months)
8.	44	Chronic pancreatitis	02 10 84	Total	Alive
9.	66	Carcinoma	11 12 84	Head	Alive
10.	39	Carcinoma	30 05 85	Total	Alive
11.	73	Cystadenoma	20 06 85	Head	Alive
12	61	Carcinoma	19 11 85	Head	Dead (20 months)
13.	57	Chronic pancreatitis	03 04 86	Head	Alive
14.	61	Carcinoma	30 10 86	Head	Dead (5 months)
15.	31	Chronic pancreatitis	31 03 87	Head	Alive
16.	62	Carcinoma	03 09 87	Head	Alive

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a circular stapler. The common hepatic duct was anastomosed, end-to-side, to the jejunal loop, using 5/0 Ti-cron® (Cyanamid of Great Britain Ltd , UK). In the early part of the study, those patients having partial pancreatic resection had the body of pancreas anastomosed end-to-side to jejunum but in the last four patients the divided end of the pancreas was implanted into the back of the stomach.

Postoperatively, all patients had nasogastric suction using a sump tube. The jejunal loop was decompressed by a stent introduced through its blind end and passed down the lumen across the biliary anastomosis into the right hepatic duct

Recovery of gastric function was assessed in the early phase noting the duration of nasogastric suction, delay to successful introduction of a solid diet, and length of postoperative stay Postoperative complications were recorded. One patient died 10 days after her operation from a myocardial infarct, having made an otherwise satisfactory recovery. Non-fatal complications occurred in eight patients

Late gastrointestinal function was assessed 3 months after operation in 12 patients, the remaining four patients were excluded for the following reasons. early postoperative death ($n=1$); prolonged gastric stasis, necessitating further surgery ($n=2$); and persistent pancreatic sepsis and fistula ($n=1$).

Late function was assessed by ability to regain weight after operation, frequency of bowel motions and the requirement for pancreatic supplements. Absorption was measured by 3-day faecal fat estimations on a 'normal home diet', and gastric emptying of a standard mixed meal was measured by a dual isotope technique. Normal liquid emptying is exponential with 50 per cent emptying occurring between 15 and 20 min after ingestion; normal solid emptying is linear at 0 8–1 0 per cent clearance per min Validation studies for this test have shown that 95 per cent of normal subjects empty within these two ranges and rates outside these limits are considered abnormal Late complications were noted.

Results

Early function

In considering early gastric function (*Table 2*), the patients fall clearly into two groups. In the nine patients who had no abdominal complications other than gastric stasis after operation and in the patient who died subsequently from an infarct, the duration of nasogastric aspiration ranged from 4 to 25 days. Of these ten patients, seven had their nasogastric tube removed by the eighth day and another had it removed on the tenth day. Each of these progressed to a solid diet between 1 and 5 days later, with the latest commencing a solid diet on the 15th postoperative day and the earliest on the fifth postoperative day. Two patients without evidence of any other intra-abdominal complication had prolonged gastric stasis (18 and 25 days) with large volumes of gastric aspirate (>1000 ml/day). Both eventually required gastric bypass. At operation, the stomach was unremarkable and the duodenojejunal anastomosis appeared to be healing satisfactorily. In the first patient (No. 6), no mechanical reason for the delay was found Because he had had a previous Roux-en-Y choledochojejunostomy, the duodenojejunal anastomosis was technically more difficult and it was assumed that the additional mobilization of the pylorus and duodenum had denervated the sphincter. In the second patient requiring bypass (No. 14), the duodenum which had been anastomosed to the left aspect of the jejunal limb had rolled across towards the right causing torsion/angulation obstruction of the jejunum immediately distal to the duodenojejunal anastomosis. Local inflammatory reaction prevented simple correction of this rotation and the problem was corrected by jejunojejunal anastomosis. Although they both made a satisfactory recovery, the complication extended their hospital stay to 34 and 39 days respectively.

The second group contains those patients who developed other intra-abdominal complications (*Table 2*). In some, the nasogastric tube was successfully removed at an early stage but either had to be reinserted or there was significant delay in the introduction of a solid diet. In fact, the first indication of an intra-abdominal complication in some of these patients was food intolerance or gastric stasis. For those with uncomplicated postoperative recovery, the median length of stay was 14 days, with a range of 11–22 days. For the patients with intra-abdominal complications, the length of stay ranged from 27 to 183 days, with a median of 39 days.

Late function

All of the patients had lost weight before operation and many could not give an accurate estimate of their normal body weight. Of the 11 patients followed to 3 months, nine showed significant weight gain ranging from 2 to 10 kg. In three patients, the weight remained static.

Nine patients reported passage of normal stools once or twice each day. In the other three, bowel frequency was increased but only one of the three patients described steatorrhoea. At the time of writing, only four patients are regularly taking pancreatic supplements. However, the discovery of significant osteoporosis in the first patient, a man aged 53 at the time of his operation, has led to a more aggressive policy with the use of pancreatic supplements.

Faecal fat estimations performed on a normal home diet without pancreatic supplements in 12 patients gave a median faecal fat excretion of 12·9 g/day (range 1·8–42·1 g). Four of the patients (two having had total pancreatectomy) gave values within the normal range (less than 7 g fat/day). Four patients had faecal fat excretion of between 12 and 14 g per day and each reported passing normal stools with normal frequency and took no pancreatic supplements. Two of these four had had total pancreatectomy. Four patients had frank steatorrhoea and three of the four accepted advice to take pancreatic supplements.

Table 2 *Details of early postoperative function in 16 patients having pylorus-preserving pancreatectomy*

Patient	Operation	Nasogastric tube out	Commencement of solid diet (days)	Postoperative stay (days)	Complication
1.	Total	4	5	21	Nil
2.	Total	6	10	11	Myocardial infarct (fatal)
3.	Head	7+	Delayed	52	Pancreatic fistula
4.	Total	4	Delayed	42	Subphrenic
5.	Head	6	9	14	—
6.	Head	25	—	34	Stasis
7.	Head	9+	Delayed	183	Pancreatic abscess
8.	Total	6	10	39	Subphrenic
9.	Head	10	15	22	—
10.	Total	5	6	11	—
11.	Head	6	9	14	—
12.	Head	12+	Delayed	35	Pancreatic leak
13.	Head	7+	Delayed	27	Haematemesis
14.	Head	18	—	39	Stasis
15.	Head	8	10	15	—
16.	Head	6	8	11	—

+ Indicates nasogastric tube reinserted

Table 3 *Details of late postoperative function in 16 patients having pylorus preserving pancreatectomy*

Patient	Weight change (kg)	Bowel movements (per day)	Pancreatic supplements	Faecal fat (g/day)	Gastric emptying Solid	Gastric emptying Liquid	Complication
1.	+2	1–2	–	13·0	—	—	Duodenal ulcer, osteoporosis
2.	—	—		—	—	—	
3.	+4	1–2	–	13·5	r	r	—
4.	0	2	–	5·3	—	—	
5.	+4	1–2	–	1·8	—	—	
6.	—	—		—	—	—	Duodenal ulcer
7.	—	—		—	—	—	
8	+10	4–6	+	2·7	r	r	—
9	0	1–4	+	28·8	n	n	—
10	+2	1–2	–	12·7	n	n	—
11.	0	2–3	+	37·1	n	n	—
12.	+4	1	–	42·0	s	s	—
13.	+2	1	–	12·9	n	n	—
14	—	—		—	—	—	Duodenal ulcer
15.	+4	1–2	+	42·1	s	n	Small bowel obstruction
16	+6	0–2	–	5·6	n	n	—

r, Rapid; n, normal, s, slow

One refused to take the supplement, but gained weight and reported normal stool function after she was treated with an H_2-receptor antagonist.

Gastric emptying was measured at 3 months in nine patients in the latter part of the study. No consistent pattern emerged and there was no correlation between the delay to recovery of gastric emptying after operation and the rate of emptying measured 3 months later. This assessment is confused by the fact that postoperative complications appeared to be associated with early stasis in a number of these cases.

Late complications, probably related to the operation, have been observed in four patients. Three patients have developed endoscopically confirmed duodenojejunal ulceration presenting with bleeding; each required transfusion but did not require further surgery. Included in this number are the two patients who had prolonged early stasis necessitating a surgical procedure. In neither case had a vagotomy been performed. The third patient, 5 years after his operation, developed a jejunal ulcer which healed on H_2-receptor antagonist therapy. Also, he developed severe osteoporosis resulting in a compression fracture of T_{12}. In the fourth patient, a further laparotomy was required for small bowel obstruction.

Of the five patients who have died from recurrent carcinoma, none has shown evidence of involvement of the duodenal bulb to indicate compromised clearance. Each of these five patients had multiple liver metastases; in two cases these were heralded by unstable diabetes. In addition, three patients had retroperitoneal recurrence presenting with unremitting pain. Review of the histology in these three cases showed perineural or perilymphatic tumour involvement adjacent to the tumour yet only one of the three had positive lymph node involvement in the resected specimen.

Discussion

Our results show that it is not possible to make dogmatic predictions about the outcome in individual cases following pylorus-preserving pancreatectomy. In the early phase, most of the patients with delayed emptying also suffered an intra-abdominal complication In only two of the seven with significant early delay in emptying was there no extragastric cause. In the first of these two patients (No. 6), previous surgery for chronic pancreatitis had included a choledochojejunostomy for bile duct obstruction and it is possible that this interfered with the reconstruction. In the second patient, there was complete obstruction of the jejunum immediately distal to the duodenojejunal anastomosis apparently secondary to a form of torsion. A similar torsion effect has been observed by other surgeons (personal communication) but whether this is the cause of the gastric stasis or secondary to gastric dilatation is uncertain. Other authors[7,8,10,11] have reported a variable frequency for delayed emptying but it is not clear from most of these papers whether the delay occurred in patients making an uncomplicated recovery, or in those with significant complications. The time to removal of the nasogastric tube, commencement of early diet and length of postoperative stay in our uncomplicated patients is shorter than those reported by Warshaw and Torchiana[8], who have emphasized the frequency of early gastric stasis. Also, it is not clear from many of the discussions of the pylorus-preserving techniques whether or not the neurovascular supply to the pylorus was preserved. Cooper and Williamson[9] appear to be the only authors who have preserved the neural connections which run with the gastroduodenal artery to contribute to the plexus via the right gastroepiploic artery. They were not impressed with the benefits of this step in the four patients in whom it was used. We did not preserve the gastroduodenal artery, believing that in the patients with cancer, the trunk of the artery should be removed with the pancreas. However, in patients with benign disease, there is probably no reason why it could not be preserved.

In the early part of the study, where the standard pancreaticojejunal anastomosis employed for the Whipple reconstruction in our department over many years was attempted, there was an unexpected rate of leakage (*Table 2*). In the last four patients, where pancreaticogastrostomy was used, that problem has not been encountered.

The results in this series with regard to late gastrointestinal function are similar to those reported by Traverso and Longmire[10] and Newman *et al.*[11]. Of further interest is the similarity between the functional results observed in these patients where the second, third, and fourth parts of duodenum were resected and the results reported by Lambert *et al.*[12] for a new operation for chronic pancreatitis where the duodenum was carefully preserved.

Bowel function was reported to be normal by the majority of patients despite the frequency of biochemical steatorrhoea (*Table 3*). Only in those patients with grossly elevated levels of faecal fat was steatorrhoea recognized to be a problem by the patient. The frequency of steatorrhoea may be reduced in some patients by resorting to a low-fat diet rather than continuing with pancreatic supplements. In the longer term, this may not be a problem but the development of significant osteoporosis in a man, 5 years after pancreatectomy, is of concern. A careful analysis of his diet indicated a very low fat intake. A number of our patients admit that they have eliminated dairy products from their diet and that their meat intake consists of steamed or grilled fish or chicken. Our results for faecal fat estimation are very similar to those reported by Traverso and Longmire[10], but a similar range of values was reported after standard pancreaticoduodenectomy by Fish *et al.*[13]. The limited data available for patients having Whipple's procedure suggest a similar wide range of results but, since it is recognized that gastrectomy alone leads to a significant increase in the faecal fat levels[14], it is conceivable that the results will be less satisfactory. Although the numbers in the present series are small, there does not appear to be any gross difference in faecal fat excretion between those patients with a normal pancreatic tissue remnant and those with chronic pancreatitis. Of note is the satisfactory fat absorption, as judged by faecal fat estimation, in the four patients with total pancreatectomy (2·7, 5·3, 12·7 and 13·0 g/day). These patients, perhaps by virtue of their diabetic state, were much more conscious of their diet and regulated their fat intake.

Gastric emptying in our patients showed a range of differences from normal. However, there did not appear to be any obvious correlation with the clinical status of the patient. Patti *et al.*[15] showed similar variations when they examined ten patients some time after pylorus-preserving pancreatectomy. Of their ten patients, six were normal, three showed rapid emptying and one, delayed emptying. Although seven of their ten patients also showed rapid small bowel transit, most were asymptomatic. There was no difference in function between those with benign disease and those with carcinoma.

While the move from pancreaticojejunal anastomosis to pancreaticogastrostomy later in this study does not appear to have influenced the long-term results it is hoped that it may have overcome some of the technical difficulties. Undoubtedly, the anastomosis to the stomach is simpler than that to jejunum. Access to the body of pancreas is limited if a technique preserving all neurovascular attachments to the stomach is utilized. The technique of pancreaticogastrostomy was described by von Reding[16] and, in a study of pancreatic function after the standard Whipple procedure but employing a pancreaticogastrostomy, Christiansen *et al.*[17] suggested that pancreatic enzymes were not inactivated in the stomach and that there was no tendency towards stenosis of the pancreatic duct. The only complication we have observed from this procedure was haemorrhage from a small artery on the lateral margin of the pancreas, which was successfully controlled by endoscopic methods.

From this study, we conclude that the functional results are satisfactory after pylorus-preserving pancreatectomy and may be an improvement on those achieved with the Whipple pancreatectomy. The mechanism for the delayed gastric emptying reported in a number of series is unclear. However, in some patients it is a reflection of perigastric inflammation or sepsis. Measures of function other than those of gastric emptying, such as acid secretion and serum gastrin levels following pylorus-preserving pancreatectomy, have been studied[18] and, by those parameters, gastric function is essentially normal. One possible explanation for the delayed gastric emptying is the observation by Barkin *et al.*[19] that as many as 60 per cent of patients with pancreatic cancer have delayed gastric emptying preoperatively. In patients with advanced pancreatic cancer, that might be explained on the basis of perineural infiltration, but that should not be the explanation for the delay in those with benign disease or localized tumour.

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C-reactive protein, antiproteases and complement factors as objective markers of severity in acute pancreatitis

C. Wilson, A. Heads, A. Shenkin and C. W. Imrie

Departments of Surgery, Immunology, and Pathological Biochemistry, Royal Infirmary, Glasgow, UK

Correspondence to:
Mr C. Wilson, Division of Surgery, Royal Infirmary, Glasgow G4 0SF, UK

In a series of patients with acute pancreatitis we have studied complement factors, antiproteases (α_2-macroglobulin and α_1-antiprotease) and C-reactive protein to determine the value of their sequential measurement in the prediction of outcome relative to clinical assessment and current multiple factor scoring systems. Complement factors were unhelpful in predicting the severity of an attack. α_2-Macroglobulin levels were significantly lower in complicated attacks during days 3–8 and α_1-antiprotease levels were significantly higher during days 4–8. C-reactive protein concentrations showed the best discrimination between mild and complicated attacks, levels rising higher and persisting for longer in complicated attacks; these differences were highly significant from day 2 (the morning after admission) to day 8. The concentrations providing the best discrimination were found to be $\geqslant 210$ mg/l for the peak C-reactive protein (on the second, third or fourth day) and $\geqslant 120$ mg/l for the C-reactive protein at the end of the first week. Analysis demonstrated both the peak or seventh-day C-reactive protein concentration to be of similar accuracy to either the Ranson or Glasgow multiple factor scoring systems and slightly better for attacks associated with gallstones. The C-reactive protein assay is simple, quick to perform, provides useful clinical information and is more likely to be of value and to be adopted into routine clinical practice than multiple factor scoring systems.

Keywords: Pancreatitis, outcome, C-reactive protein, antiproteases, complement

Edmondson and Berne in 1944 were first to suggest that measurement of a single biochemical factor, that of hypocalcaemia, might be a useful predictor of outcome in acute pancreatitis[1]. Laboratory prediction of severity in acute pancreatitis has become accepted since 1974 when Ranson *et al.*[2] described a scoring system utilizing 11 objective factors, each with significant prognostic value. Imrie *et al.*[3] in 1978 published a simplified system, modified for use in patients in the UK and based on nine factors. Multiple factor scoring systems reflect respiratory, renal, liver and haematological disturbance in the body and provide some clinically useful information but may be influenced by the patient's pre-admission state and the aetiology of the attack. The greater age of the patients and the early, transient liver dysfunction commonly associated with gallstone pancreatitis result in such patients consistently scoring higher than an alcohol-associated attack of equivalent severity. This has led to modifications being made to both major scoring systems; Ranson now describes two different scoring systems, one for gallstone and one for non-gallstone attacks[4] while the Glasgow scoring system, which has been simplified to include only eight factors[5], remains applicable to both common aetiologies of acute pancreatitis[6].

Multiple factor scoring systems have been widely used in the study of patients with acute pancreatitis, providing stratification of the risk of death or major morbidity and comparison of patients between different centres. Their complexity, however, probably limits their routine use in daily clinical practice. Neither system can be applied sequentially to monitor the course of the attack which might usefully assess the response to therapy or provide warning of a developing late complication.

Other possibly useful biochemical indicators of severity in acute pancreatitis include complement factors[7–10] and the antiproteases (α_2-macroglobulin and α_1-antiprotease)[10,11]. The value of C-reactive protein measurement in acute pancreatitis was first suggested by Mayer *et al.* in Leeds in 1984[12] and subsequently by others[10,13]. A comparative study examining the ability of multiple factor scoring systems and these individual biochemical parameters to predict outcome early in the course of the illness has not been reported, although a persistently high C-reactive protein concentration at the end of the first week appears to identify patients at risk of developing a late pancreatic collection[12].

We have undertaken a study of five complement factors, the two major antiproteases and the non-specific inflammatory marker C-reactive protein to determine the value of their sequential measurement in the prediction of outcome from acute pancreatitis relative to clinical assessment and the multiple factor scoring systems.

Patients and methods

Acute pancreatitis was initially diagnosed in all patients on the basis of a serum amylase >1200 units/l (normal range, 70–300 units/l) (Phadebas, Pharmacia Diagnostics AB, Uppsala, Sweden) and a compatible clinical picture[14]. Laboratory data were collected prospectively from all patients to permit scoring of both the Ranson and Glasgow multiple factor systems. As the aetiology of the attack was not usually apparent on admission, the original Ranson scoring system has been used throughout[2].

Blood samples were taken on the day of admission (day 1) and each morning thereafter until day 8 or until discharge if sooner. Samples were centrifuged and frozen within 60 min of venepuncture. Complement factors were measured on plasma samples stored at −60°C until analysis. C3 and C4 were measured by radial immunodiffusion (Behring Diagnostics, Hounslow, Middlesex, UK) and factor B by immunodiffusion using an in-house prepared agar plate containing antihuman properidin factor B (Atlantic Antibodies, Winnersh, Berkshire, UK). C1q and C3d were measured on a Beckman ICS nephelometer using antihuman C1q (Atlantic Antibodies) and antihuman C3d (Dako Ltd., High Wycombe, Buckinghamshire, UK) according to the method of Vergani[15]. Anti-

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proteases and C-reactive protein were measured on serum samples stored at −20°C before analysis. α_2-Macroglobulin and α_1-antiprotease were measured by turbidimetric immunoassay (Atlantic Antibodies). C-reactive protein was measured by a fluorescence polarization immunoassay (Abbott TDX, Abbott Laboratories Ltd, Wokingham, Berkshire, UK). Normal complement and acute phase protein ranges were established on 30 and 100 normal controls respectively

The patients studied fell into two groups: 30 patients had complement factors assayed and 72 patients had antiproteases and C-reactive protein assayed The first 50 patients who had antiproteases and C-reactive protein measured were studied consecutively; the remaining 22 were selected for study from the next 60 patients admitted, having been judged as having moderate or severe pancreatitis on the basis of a clinical assessment on admission. Clinical assessment was repeated at 24 and 48 h; those judged to have severe pancreatitis on assessment were considered at risk of death or of developing a complication.

Complicated attacks of acute pancreatitis were defined as resulting in death or a local pancreatic complication: abscess, pseudocyst or necrosis (defined as necrotic pancreatic and/or peripancreatic tissue recovered at laparotomy or post mortem). Nine additional patients manifested acute respiratory insufficiency defined as a $P_{O_2} < 60$ mmHg, requiring oxygen by mask for more than five consecutive days (mean, 8 days). Each had a prolonged, clinically severe illness with a mean hospital stay of 20 days, although ultrasound scanning in each failed to demonstrate local pancreatic complications. Nine (30 per cent) of the patients whose complement factors were measured had a complicated attack with two deaths (7 per cent) compared with 25 (35 per cent) and ten deaths (14 per cent) respectively for those having antiproteases and C-reactive protein measured.

Statistical analysis was performed using the Mann–Whitney *U* test.

Results

Complement factors C3 and factor B concentrations showed an early fall followed by a sustained rise during the course of the illness in both mild and complicated attacks, factor B rising above the normal range in both groups of patients. The individual results showed a wide scatter and no difference emerged between mild and complicated attacks. C4 concentrations showed no significant changes in either mild or complicated attacks through the course of the illness. C1q levels fell during the attack, falling below the normal range in complicated attacks, but these differences failed to reach statistical significance. C3d levels (a product of C3 activation) were increased in 33 per cent of patients at some time during their illness, thus indicating complement activation, but this could not be related to the severity of the attack judged clinically or on multiple factor scoring.

α_2-Macroglobulin levels fell during the attack, with levels significantly lower in complicated attacks between days 3 and 8 (*Figure 1*). α_1-Antiprotease levels rose during the attack in both mild and complicated attacks, with levels significantly higher in complicated attacks between days 4 and 8 (*Figure 2*).

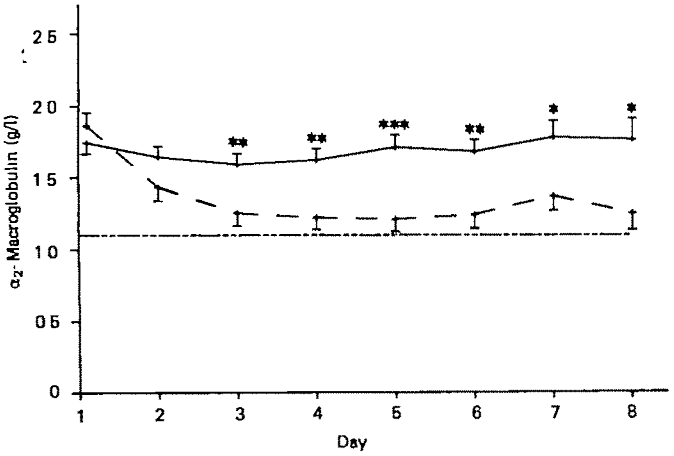

Figure 1 *Sequential α_2-macroglobulin concentrations in 47 patients with mild pancreatitis* (——) *and 25 with complicated attacks* (– – –). *Results are expressed as mean ± s e m.*, * P<0·05; ** P<0·01, *** P<0·001 (*mild* versus *complicated*); – – – —, *lower limit of normal for α_2-macroglobulin*

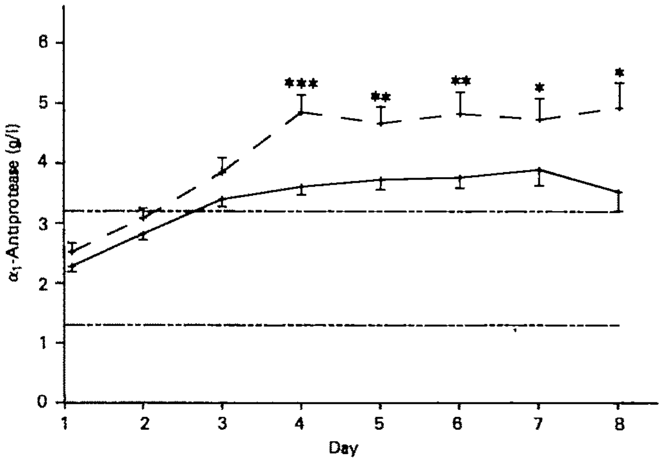

Figure 2 *Sequential α_1-antiprotease concentrations in 47 patients with mild pancreatitis* (——) *and 25 with complicated attacks* (– – –) *Results are expressed as mean ± s e.m.*; * P<0 05, ** P<0 01, *** P<0·001 (*mild* versus *complicated*); – – – —, *normal range of α_1-antiprotease*

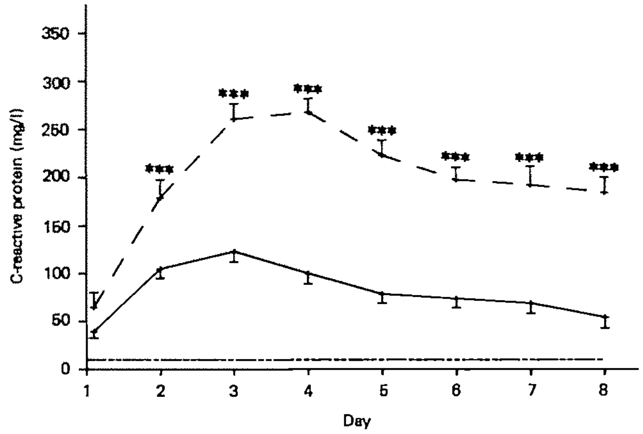

Figure 3 *Sequential C-reactive protein concentrations in 47 patients with mild pancreatitis* (——) *and 25 with complicated attacks* (– – –) *Results are expressed as mean ± s e.m.*, * P<0 05; ** P<0 01, *** P<0 001 (*mild* versus *complicated*); – – – —, *upper limit of normal for C-reactive protein*

C-reactive protein levels provided the best discrimination, with levels markedly higher and persisting for longer in those with complicated attacks, these differences were highly significant from day 2 (the morning after admission) to day 8 (*Figure 3*). C-reactive protein, therefore, was shown to be the best of all the factors tested for sequential monitoring of acute pancreatitis. Eight of the 11 patients subsequently developing pancreatic necrosis or pseudocyst had a peak C-reactive protein concentration of ≥300 mg/l. However, the mean C-reactive protein concentration did not distinguish these 11 patients (six of whom ultimately required surgery) from nine patients with acute respiratory insufficiency, all of whom had a severe illness but settled without surgery (*Figure 4*). C-reactive protein levels did not predict death in three elderly patients who died from shock on the second day of admission.

The C-reactive protein concentration providing the best discrimination (combining the highest sensitivity and specificity) was determined both for the peak C-reactive protein (occurring between the second and fourth day of illness) and for the concentration at the end of the first week. The best discrimination was found with a peak C-reactive protein concentration of ≥210 mg/l and, at the end of the first week, ≥120 mg/l (*Figures 5* and *6*). Applying these levels to the data permitted comparison of the prognostic value of C-reactive protein measurement with clinical assessment and the multiple factor scoring systems. *Table 1* shows both the peak and 7-day C-reactive protein concentrations to be of similar accuracy to either the Ranson or Glasgow multiple factor scoring systems.

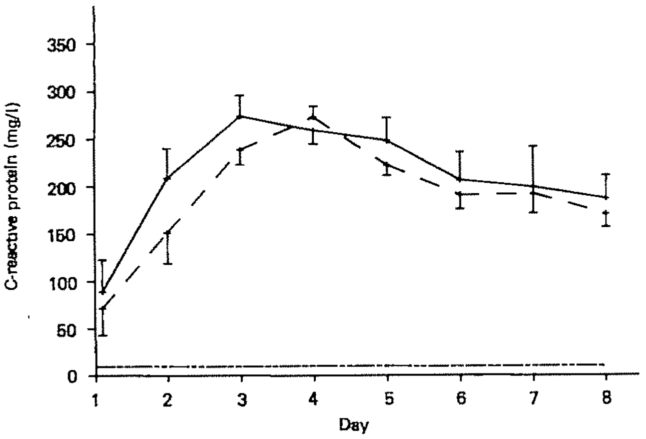

Figure 4 *Mean C-reactive protein concentrations in 11 patients with pancreatic necrosis or pseudocyst (——) and nine patients with acute respiratory insufficiency (– – –). -·-·-, Upper limit of normal for C-reactive protein*

Table 1 *Comparison of the peak and 7-day C-reactive protein concentrations with the Ranson and Glasgow multiple factor scoring systems*

	Sensitivity (%)	Specificity (%)	Correctly classified (%)
Peak C-reactive protein (≥210 mg/l)	83	85	85
C-reactive protein at 7 days (≥120 mg/l)	90	85	87
Glasgow score (8 factors)	76	83	81
Ranson score (11 factors)	88	79	82
Clinical assessment (on admission)	38	96	76
Clinical assessment (at 48 h)	46	98	80

Peak C-reactive protein, highest concentration on the second, third or fourth day; sensitivity, percentage of all complicated attacks predicted correctly by test; specificity, percentage of all mild attacks predicted correctly by test

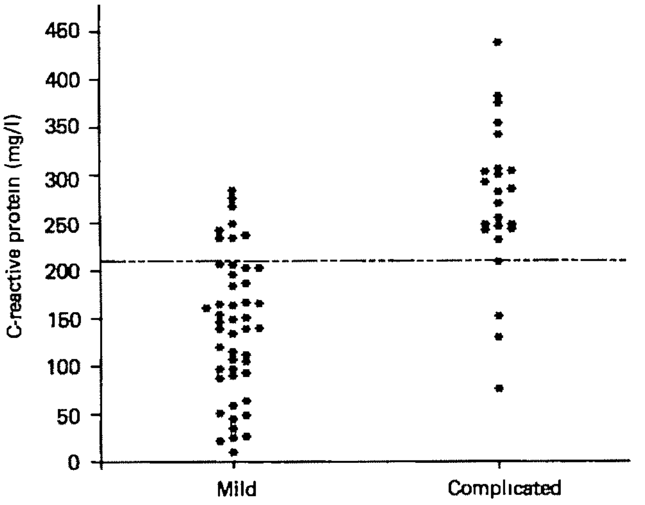

Figure 5 *Scattergram showing discrimination between mild and complicated attacks of pancreatitis based on the peak C-reactive protein concentration recorded on days 2–4. -·-·-, The peak concentration providing the best discrimination was ≥210 mg/l*

Table 2 *Comparison of C-reactive protein and multiple factor scoring systems in gallstone and alcohol-associated attacks*

Parameter	Sensitivity (%)	Specificity (%)	Correctly classified (%)
Gallstone			
Peak C-reactive protein (≥210 mg/l)	100	79	88
C-reactive protein at 7 days (≥120 mg/l)	100	100	100
Glasgow score	80	71	75
Ranson score	90	71	79
Alcohol			
Peak C-reactive protein (≥210 mg/l)	100	87	90
C-reactive protein at 7 days (≥120 mg/l)	67	86	82
Glasgow score	67	100	93
Ranson score	83	96	93

Peak C-reactive protein, highest concentration on the second, third and fourth day; sensitivity, percentage of all complicated attacks predicted correctly by test; specificity, percentage of all mild attacks predicted correctly by test

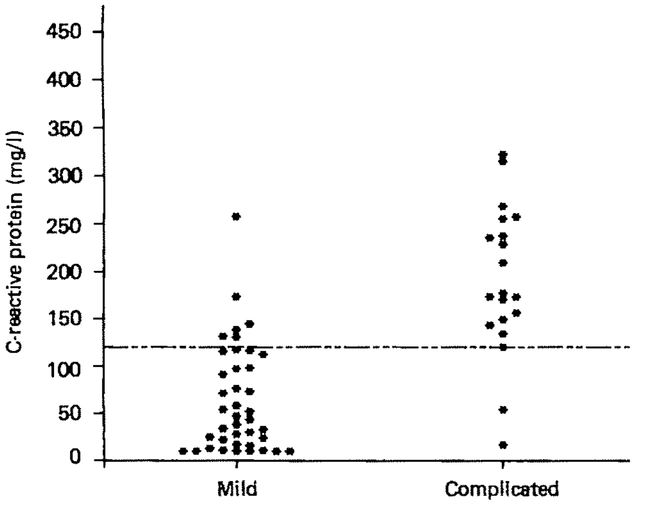

Figure 6 *Scattergram showing discrimination between mild and complicated attacks of pancreatitis based on the C-reactive protein concentration on day 7. -·-·-, The peak concentration providing the best discrimination was ≥120 mq/l*

When the aetiology of the attack was considered, C-reactive protein measurement appeared to be slightly better than either multiple factor scoring system for attacks associated with gallstones but slightly less good for alcohol-associated attacks (*Table 2*).

Although the proportion of attacks correctly predicted by clinical assessment approached that of the multiple factor scoring systems, closer examination revealed that while almost all mild attacks were identified correctly, fewer than half the patients with complicated attacks were correctly identified at 48 h.

Discussion

Clinical assessment of the severity and likely outcome of acute pancreatitis early in the course of an attack is notoriously unreliable. The accuracy of clinical assessment appears to improve with time and one study suggested that 83 per cent of severe attacks were correctly predicted 48 h after admission[16]. Our own data have demonstrated that while all patients subsequently dying were correctly identified as having a severe attack at 48 h, the overall accuracy in predicting complicated attacks was poor at 46 per cent. Clinical assessment, although an essential component of the overall monitoring and treatment of such patients, remains imprecise, subjective and non-reproducible, and the search continues for an ideal objective marker of severity in this condition.

Complement factors showed no relationship to the severity of an attack and their measurement was therefore discontinued after 30 patients had been analysed. Other workers have found complement levels, particularly C3 levels to be of value in the prediction of outcome in acute pancreatitis[7-10]. Whicher *et al.*[17] found, as we did, a wide scatter of results and no apparent relationship between the presence or absence of complement activation (as indicated by an increased C3d) and severity of the attack. The most promising of the complement factors studied was C1q. This is the first component of the classical complement pathway and its apparent consumption in acute pancreatitis is difficult to explain. Complement activation in acute pancreatitis is thought to occur by a direct attack on C3 by trypsin[18] or, as Foulis and co-workers have suggested, by the alternative complement pathway[8]. Neither should lead to consumption of the early factors of the classical complement pathway. C-reactive protein binds at sites of injury within the body and once complexed is a potent activator of the classical complement pathway, beginning with C1q[19] The fall in C1q which occurs in the more severe cases may therefore be associated with this mechanism.

Sequential measurement of the antiproteases appeared more promising, particularly α_2-macroglobulin which showed useful discrimination between mild and complicated attacks. α_2-Macroglobulin is most probably the key intravascular antiprotease. It binds irreversibly with activated proteolytic enzymes leading to a conformational change within the antiprotease molecule and its rapid uptake by the macrophages of the reticuloendothelial system. α_2-Macroglobulin does not act as an acute phase reactant since its synthesis does not increase in response to injury. The low levels of α_2-macroglobulin seen in the most severe attacks of acute pancreatitis suggest its consumption and may reflect the amount of proteolytic enzyme activation that is occurring. A proportion of the measured α_2-macroglobulin in serum in severe acute pancreatitis is in a complexed form and unavailable for protease binding[20]. The importance of low levels of this antiprotease is unclear but may have clinical relevance.

α_1-Antiprotease acts as an acute phase reactant, levels rising several-fold during the illness. The net effect is that the overall capacity of serum to bind trypsin and other activated proteolytic enzymes increases during the course of the attack[21]. The binding between α_1-antiprotease and trypsin is reversible and this complex appears to dissociate, the trypsin being taken up by α_2-macroglobulin before its clearance from the body[22]. Therefore, although the total trypsin binding capacity of serum may increase, the fall in α_2-macroglobulin may be a rate-limiting step to the clearance of proteases from the circulation. Clearance of α_2-macroglobulin–trypsin complexes by the reticuloendothelial system may also be depressed in severe acute pancreatitis[23] and, as these complexes retain proteolytic activity[24,25], this might be pathogenic in man. A recent controlled clinical trial has studied the therapeutic benefit of fresh frozen plasma in acute pancreatitis Infusion of fresh frozen plasma was able to restore α_2-macroglobulin levels in treated patients but produced no clear evidence of a beneficial effect, although too few patients with severe illness had been included to confirm this statistically[26].

In our experience the C-reactive protein concentration provided the best discrimination of all the factors investigated in the present study. C-reactive protein is a protein of uncertain role in the body. It acts as a non-specific inflammatory marker and monitoring has been shown to be of clinical value in a number of conditions[19]. C-reactive protein is usually present in low concentrations in the bloodstream It is synthesized in hepatocytes, elevated serum levels being detected about 8 h after injury and reaching a peak some 24–48 h later. The delay until peak levels are attained may account for the failure of C-reactive protein to detect the risk of early death in three patients in this study.

Beger's group has suggested, on the basis of a rather limited study of 35 patients, that a C-reactive protein concentration >100 mg/l correctly predicts pancreatic necrosis in 95 per cent of cases[10], these patients having necrosis confirmed at subsequent laparotomy. We cannot agree with this view as in our practice this level would result in 57 (79 per cent) of the 72 patients reported here having 'pancreatic necrosis' predicted. We have found that while a cut-off level of ≥210 mg/l (more than twice that described by Beger's group) identifies a group of patients with severe pancreatitis, it was clearly not specific for the presence of pancreatic necrosis. While a number of the patients in our severe group may have had unsuspected pancreatic necrosis manifesting only as acute respiratory insufficiency, the clinical improvement that occurred without recourse to surgery suggests that Beger's group has a lower threshold for surgery and may be operating unnecessarily in some patients.

The assay for C-reactive protein is simple and quick and we have demonstrated that measurement of C-reactive protein is at least as accurate as either of the multiple factor scoring systems and probably better for gallstone-associated attacks, which presently account for more than 50 per cent of patients in the UK. In practice, a peak C-reactive protein ≥300 mg/l and/or persistent elevation at the end of the first week, as was originally shown by the Leeds group[12], provide useful warning of the development of local pancreatic complications. Such a test would clearly be of clinical value in selecting patients for investigation by expensive imaging techniques, such as contrast-enhanced computed tomography; it would select those patients who might usefully be monitored in an intensive care unit, or those in whom parenteral nutrition may be indicated if the attack appears to be slow in settling. The complexity of multiple factor scoring systems has probably limited their routine use and measurement of a single factor, such as C-reactive protein, appears more likely to be adopted into daily clinical practice.

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Characterization of breast cancer subgroups in an African population

A. A. Otu, I.-O. A. Ekanem*, M. I. Khalil*, M. D. Ekpo* and E. B. Attah*

*Departments of Surgery and *Pathology, College of Medical Sciences, University of Calabar, Calabar, Nigeria*

Correspondence to: Mr A. A. Otu

A detailed prospective study of 58 consecutive breast cancer patients and contemporaneous controls, using age, duration of tumour and presence or absence of poor prognostic signs as clinical parameters, clearly showed that the patients fell into three distinct groups. Group A accounted for 30 per cent of cancers and consisted of young women (21–45 years) with advanced cancers, a short history (3 months or less) and poor prognostic signs; these patients had fast-growing tumours. Group B, to which nearly 60 per cent of patients belonged, was made up of menopausal women (46–50 years) with advanced disease, a history of from 3 months to 1 year and poor prognostic signs; their tumour growth rate was intermediate. Group C made up slightly more than 10 per cent of cases and consisted of postmenopausal women (50 years and above) who gave a long history (1 year or more), and had resectable tumours without poor prognostic signs. Thus, although advanced breast cancer in tropical Africa is due to late presentation in the majority of cases, a small but significant proportion of women have advanced disease in spite of early presentation, attributable to fast tumour growth rate.

Keywords: Breast cancer, prognostic signs

In tropical African countries most breast cancer patients seek hospital treatment when the disease is far advanced; consequently little can be done and the prognosis is uniformly poor[1–3]. This contrasts markedly with reports of early resectable disease in western countries where tumours are increasingly being diagnosed by mammography and treated before they become clinically palpable[4,5]. Generally, African patients present late and the temptation has been strong to attribute the extensive breast cancers to late presentation. The present prospective study reviews consecutive patients seen at the University of Calabar Teaching Hospital in the 5-year period from January 1980 to December 1984 A detailed investigation of patients and contemporaneous controls with benign breast lesions was conducted using the clinical criteria of age, duration of tumour, presence or absence of those physical signs known to be associated with poor prognosis, and tumour resectability. The study has attempted to determine whether late presentation is solely responsible for advanced tumours and to provide preliminary data concerning breast cancer for further exploration. Clinical methods of investigating breast cancer are still very important and relevant in this region with comparatively low levels of technology and where sophisticated investigative tools are not available.

Patients and methods

The study was conducted in the 5-year period from January 1980 to December 1984 during which 259 consecutive patients with breast tumours attended the University of Calabar Teaching Hospital, Calabar A detailed clinical history with particular attention to the duration of the tumour was obtained from each patient, this was followed by physical examination with emphasis on those physical signs that are known to be associated with extensive disease and carry a poor prognosis, as described by Haagensen[6]

A plain X-ray of the chest was taken and, where indicated, a skeletal survey was conducted. Haemoglobin, total white cell count and differential were obtained. Age-matched female patients with benign breast lesions provided contemporaneous controls to women with breast cancers An excision or incision biopsy of each breast tumour was taken where applicable and paraffin sections stained with haematoxylin and eosin were examined histologically Further local treatment, where indicated, consisted of simple mastectomy with ipsilateral axillary node sampling. All patients were followed up until lost to follow-up or death, a period of 1–5 years.

Results

Incidence of breast cancer

Of the 259 patients seen, 69 (26·6 per cent) had malignant breast tumours and 190 (73·4 per cent) had benign tumours. Of the 69 malignant tumours, 67 (97 per cent) were breast cancer; two were Burkitt's tumour (African childhood lymphoma) in children aged 1 and 16 years.

Sex incidence

Nine of the 67 (13 per cent) breast cancer patients were male, giving a male:female ratio of 1 7. Features of the disease in the nine male patients are reported elsewhere.

Age incidence

Figure 1 shows the age distribution of the 58 women with breast cancer. The age ranged from 21 to 70 years with a mean of 40 years. The peak incidence is biphasic. an early peak occurs in the 26–35 years group and a late and even higher peak occurs in the 46–50 years group. Over half of the women were aged 40 years or less and 12 (21 per cent) were 30 years or younger.

Poor prognostic signs

Matted or ulcerated lymph nodes in the ipsilateral axilla were seen in 51 of 58 (88 per cent) cancer patients, ulcerated tumours in 41 (71 per cent) patients, and peau d'orange in 38 (66 per cent) Other poor prognostic signs included fixation of the cancer to the chest wall in 27 (47 per cent) patients and total breast involvement by tumour, lymphoedema of the upper extremity, and distant metastasis in 18 patients each.

Duration of tumour

Patients were categorized into three groups based on the duration of tumour: duration of tumour 3 months or less, duration of tumour from greater than 3 months to 1 year, and duration of tumour greater than 1 year. Seventeen (29 per cent), 33 (57 per cent) and eight (14 per cent) patients respectively belonged to the three groups.

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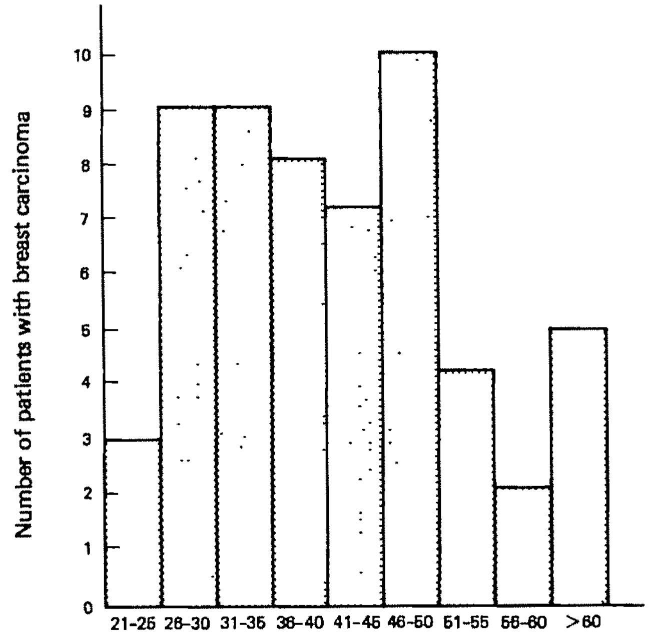

Figure 1 *Histogram showing age distribution of 57 of the 58 patients with breast cancer*

Table 1 *Histological types of breast carcinoma in 58 patients*

	No. of patients	Percentage
Infiltrating ductal	38	66
Medullary	8	14
Scirrhous	7	12
Scirrhous with medullary	2	3
Mucinous	3	5

Fertility and parity

Of the 58 patients, 56 (97 per cent) were multiparous: the other two patients were nulliparous. The number of children born ranged from two to ten with a mean of five. All the patients had successfully breast-fed their infants for periods ranging from 3 months to 2·5 years.

Histological types of cancer

The histological types of cancer are shown in *Table 1*, the commonest type of tumour was the infiltrating ductal tumour seen in 38 (66 per cent) patients. Associated intraduct carcinoma *in situ* was seen in five cases and lobular carcinoma *in situ* in one case.

Side and site

The right:left ratio was 4.3, thus giving a slight right to left preponderance. The commonest tumour site was the upper outer quadrant, seen in 17 of 58 patients.

Age at menarche and menopause

The mean age at menarche was 12·1 years in cancer patients and for non-cancer patients it was 12·0 years. The age at menopause was 42·1 years for cancer patients and 42·2 years for controls.

Tumour growth characteristics

By combining age, presence or absence of poor prognostic signs, and duration of symptoms, the patients could be allocated to three distinct groups (*Table 2*).

Group A (16 patients) were those who were aged 21–45 years, had a tumour duration of less than 3 months and in whom one or more poor prognostic signs were present at first presentation. These signs were present even though the tumours had been present for less than 3 months, so the rate of growth of tumour in these patients was fast. In contrast, seven patients in group C aged over 50 years with tumour duration of more than 1 year had no poor prognostic signs; the growth rate of tumour in this group of patients was slow. Between these two distinct groups was a third group of patients (group B: 33 patients) aged between 46 and 50 years with tumour duration of more than 3 months but less than 1 year and poor prognostic signs at first presentation; the growth rate of tumour in this group was intermediate.

Survival

Only eight of the 58 patients (14 per cent) were alive at 5 years; one belonged to group A and seven to group C. In contrast, 56 of the 58 (97 per cent) controls were alive at 5 years; two controls were lost to follow-up and were presumed dead.

Discussion

In this African population, breast cancer is predominantly a disease of young women compared with series from western countries. Two peaks of incidence are discernible; an early peak made up of young patients in the 26–35 years group and a late and even higher peak consisting of older patients in the 46–50 years group

The majority of women presented with advanced disease, these women had come to hospital as a last resort seeking treatment that could rid them of their malodorous ulcerated tumours and make them acceptable in their homes and community. This finding corroborates with those of previous reports[1,7].

Using the criteria of age, tumour duration[8] and the presence or absence of poor prognostic signs, patients were classified into three distinct groups. Two groups exhibited poor prognostic signs and their cancers were beyond surgical extirpation. In contrast patients in the third group were without poor prognostic signs and had improved survival.

The impression in this and other tropical African countries is that breast cancer patients present with advanced tumours because they report to hospital late[2,6,7] This was true of group B patients who constituted nearly 60 per cent of patients in the present study. However, there was a distinct group of patients who at first presentation showed extensive disease in spite of a short history; these patients belonged to group A and accounted for approximately 30 per cent of breast cancer cases.

To improve the outlook for patients with breast cancer in tropical Africa, as in the West, earlier presentation is required In

Table 2 *Patient classification of tumour growth rate*

Group	No. of patients	Growth pattern
A	16 (29)	Age 21–45 years Tumour duration less than 3 months Poor prognostic signs present Fast tumour growth
B	33 (59)	Age 46–50 years Tumour duration from 3 months to 1 year Poor prognostic signs present Intermediate tumour growth
C	7 (12)	Age over 50 years Tumour duration over 1 year Poor prognostic signs absent Slow tumour growth

Percentages are given in parentheses

western countries current policy is aimed at reducing breast cancer mortality through population screening concentrated on the 50–64-year-old group by single-view mammography[5,9] as recommended by the World Health Organization[10]. However, African countries have inadequate medical facilities and low levels of technological development; they are unlikely to be able to afford mass screening. Measures aimed at early detection and prompt treatment of breast cancer in this region are urgently required and will require increased awareness of the disease in the population at risk. The findings of this study suggest that health promotion exercises should be aimed at women aged over 40 years in the first instance.

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Residual tumour after biopsy for non-palpable ductal carcinoma in situ of the breast

Th. Wobbes,
J. G. M. Tinnemans* and
R. F. van der Sluis

*Department of General Surgery, St. Radboud University Hospital, Nijmegen, and *Academic Medical Centre, Amsterdam, The Netherlands*

Correspondence to:
Dr Th. Wobbes, Department of General Surgery, University Hospital, Nijmegen, PO Box 9101, 6500HB Nijmegen, The Netherlands

In a group of 40 patients with non-palpable ductal carcinoma in situ *(DCIS) of the breast, 41 breast specimens were available for studying residual tumour after biopsy. In one group of ten patients seen before 1977, simple histological examination revealed a 9 per cent incidence of residual tumour. However, after thorough examination residual foci of DCIS were found in 77 per cent of a subsequent group of 30 patients. This means that the majority of patients would have had to undergo reoperation if a breast-saving procedure had been performed. This fact must be taken into account when planning treatment of patients with non-palpable DCIS.*

Keywords: Ductal carcinoma *in situ*, breast cancer, residual tumour

Ductal carcinoma *in situ* (DCIS) or non-invasive ductal carcinoma of the breast is a challenging problem to the surgeon. There is continuing discussion in the literature regarding how to cope with this type of lesion. After biopsy alone 30–40 per cent of the patients may develop an invasive carcinoma[1–4]. With the increasing use of mammography in the detection of breast cancer, the surgeon is confronted more and more with lesions such as microcalcifications, which may be the only sign of DCIS[5]. Now that breast-conserving surgery is finding general acceptance in the treatment of invasive carcinoma it is necessary to evaluate some results in patients with DCIS in the light of this therapy.

We have analysed the data of patients with a non-papable form of DCIS in order to throw light on the problem of residual tumour after biopsy.

Patients and methods

The present study comprised 40 women aged 35–69 years, with a mean age of 53 years, treated in the period 1971–87 The breast lesion was non-palpable and detected by mammography, either in patients drawn from a population screening project (20 cases) or in patients who were examined because of symptoms (17 cases) or in patients who were followed after mastectomy (three cases). The latter three patients were treated 1–7 years earlier because of an invasive carcinoma or DCIS of the contralateral breast; one patient had synchronous bilateral non-palpable DCIS.

Until 1977 the non-papable lesions detected in ten patients (11 breasts) were dealt with by blind biopsy. Since that time preoperative needle localization was used with a self-retaining barbed guide wire[6].

After biopsy, specimen radiography was obtained in all cases. Basically, the biopsy procedure aimed to remove all of the clustered microcalcifications Because in cases of DCIS treatment consisted of an ablative form of surgery, the specimen was investigated only for diagnosis and no margins were studied. In 12 patients a simple mastectomy (one patient bilaterally) and in 28 patients a modified radical mastectomy was performed.

Thus 41 mastectomy specimens were available for study. In 30 cases Egan's method, correlating clinical, radiographic and pathological findings was used[7]. The breast was chilled overnight in a refrigerator at 2°C and sectioned microscopically at 5-mm intervals. Then a radiogram was made of the specimens. Radiologically suspected lesions were investigated histologically. In total, 15–20 blocks were obtained

In the other 11 cases dealt with in the period up to 1977, multiple biopsy samples were taken from all the quadrants of the removed breast.

Results

In all patients except one, mammography was carried out. Clustered microcalcifications were the only findings in 35 breasts. In four, a circumscribed mass with microcalcifications was found. In only one patient was a circumscribed mass without microcalcifications seen on the mammogram.

Residual tumour after biopsy was found in 24 of the 41 breast specimens (59 per cent). Residual tumour adjacent to the biopsy area was noted in only one of the ten patients (11 breast specimens, 9 per cent) who underwent a blind biopsy before 1977. In these patients radiological findings were not correlated with pathological findings.

In 23 of the 30 breast specimens (77 per cent) in which the lesion was localized preoperatively and where Egan's method of serial whole organ sectioning was used for investigation, residual foci of tumour were detected. In 11 of the 23 patients in this group the residual tumour was located adjacent to the biopsy area (48 per cent). In four patients, foci of DCIS were found in the quadrant in which the microcalcifications were located; in eight cases the tumour extended into two quadrants of the breast.

In 19 cases a comedo type of DCIS was found and in 22 a combination of papillary, cribriform and comedo type. There were no obvious differences in histological type between the groups with and without residual tumour.

Two patients had to be treated for invasive carcinoma of the contralateral breast after an interval of 16 and 19 months respectively. In none of the 28 patients who underwent a radical or a modified radical mastectomy were axillary lymph node metastases found. In the 12 patients treated by simple mastectomy, no regional recurrence was observed in a follow-up period ranging from 8 to 16 years.

Discussion

Non-palpable DCIS is probably an important precursor of invasive carcinoma. The only method to detect these non-palpable lesions is mammography, which finds more and more acceptance as a valuable tool in detecting mammary carcinoma at an early stage of disease. Clustered microcalcifications are a strong indicator of DCIS and every surgeon charged with the care of breast cancer patients will proceed to biopsy in such patients. However, these microcalcifications in DCIS are usually only part of a tumour which may be more extensive and not visible mammographically. In our series DCIS was left behind in almost 60 per cent of the patients after excision of the microcalcifications.

An important issue is the method used by the pathologist to establish the extent of the foci of tumours. When the breast specimens were studied according to Egan's method[7], residual tumour was found in 77 per cent of the cases, while in the breasts

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studied by random sampling from all quadrants, foci of DCIS were detected in only 9 per cent of cases. Possibly the preoperative localization procedure has contributed to this high percentage of residual disease, because the specimen subsequently taken at biopsy may be smaller and more directed to the microcalcifications than that removed by 'blind' biopsy.

In the literature the incidence of development of invasive carcinoma after local excision of DCIS (palpable and non-palpable) varies from 28 to 67 per cent and such invasive growth is caused by outgrowth of residual tumour[3,8,9]. At present it is questionable whether radiotherapy can reduce the risk of development of an invasive carcinoma from DCIS. The argument against radiotherapy is supported by Schnitt and coworkers in 1984 who found in a series of 154 patients with invasive carcinoma and breast-saving treatment that the local recurrence rate was significantly increased when invasive cancer was found in combination with DCIS[10]. Moreover, interpretation of a mammogram is easier in a non-irradiated breast than in a breast that has become fibrotic following radiotherapy. It is conceivable that detection of recurrence may be delayed in such irradiated breasts.

We have to realize that in non-palpable DCIS we have the opportunity to cure the patient by mastectomy. If the opportunity to carry out mastectomy is missed, is follow-up able to detect a small invasive carcinoma at an early enough stage that the patient can still be treated curatively? The only method of detecting such early recurrence is mammography, and it is questionable whether the tumour will present again with microcalcifications. The question of whether it is justified to excise the lesion and wait will have to be answered in time as a growing number of patients are treated by breast-conserving surgery[11].

If breast-conserving therapy is contemplated, all non-invasive tumour should be excised in order to minimize the risk of malignant transformation into invasive tumour. In that event the patient has to be operated on a second time, firstly because the biopsy procedure is not able to excise all tumour and secondly because it is not justified to make the diagnosis of DCIS solely on the basis of frozen section examination[12]. It is also important to determine whether all the microcalcifications are located in the biopsy specimen and to define where other foci might be expected. Exact documentaton of the orientation of the specimen in relation to the surrounding breast tissue is necessary to obtain an accurate impression of the extent of the lesion.

Theoretically, our data suggest that wide excision or quadrantectomy would be sufficient to remove all *in situ* lesions in some three-quarters of the patients. The problem is that one is never sure of having removed the affected segment, especially in patients with multicentric DCIS. In patients with a palpable tumour the surgeon may have some landmarks, but in a non-palpable lesion one cannot be certain that the mammographically detected lesions are located in the centre of the specimen. Thorough histological examination may indicate whether more foci of DCIS are to be expected in the surrounding breast tissue and in what direction the re-excision has to be done. If one pursues histological clearance of tumour this procedure is necessary and is a factor that must be taken into consideration before any trials are commenced.

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Follow-up after treatment of primary breast cancer

This study evaluates the usefulness of routine follow-up of breast cancer patients. In all, 416 patients who were treated with curative intent for breast cancer were followed according to a fixed follow-up schedule for a minimum of 2·5 years and a maximum of 13·5 years (mean about 5 years). During the 4533 routine out-patient visits, 4116 chest radiographs, 3889 pelvic radiographs and about 17 000 laboratory tests were carried out routinely. In the follow-up period, 148 patients were found to have distant recurrence of whom 34 (23 per cent) had asymptomatic metastases and 114 symptomatic metastases. Of the 8005 routinely performed radiographs, 24 (0·3 per cent) revealed asymptomatic metastases, and the 17 000 laboratory tests led to the discovery of six asymptomatic bone and four asymptomatic liver recurrences. Screening for metastases did not result in a reduction of the lead time to the diagnosis of asymptomatic metastases; the disease-free interval was equal in both symptomatic and asymptomatic patients. Of the 46 locoregional recurrences 42 were found by physical examination during a routine follow-up visit and 37 had not been noticed by the patient. Seventeen second primary breast cancers were diagnosed, six of which were in stage I (<2 cm). Mammography was not a part of the routine follow-up scheme. It is concluded that routine follow-up of breast cancer patients by history and physical examination is sufficient to detect local recurrence and a second primary tumour as well as giving the opportunity to track signs and symptoms of distant recurrence at an early stage. Performing annual or biannual mammography is advisable, but the use of other costly routine investigations in the follow-up is not justifiable, as no therapeutic advantages can be expected.

Keywords: Breast cancer, follow-up, routine investigations

**E. J. Th. Rutgers,
E. A. van Slooten and
H. M. Kluck***

*Department of Surgical Oncology,
The Netherlands Cancer Institute,
Amsterdam, and
*Department of Surgery, St. Joseph
Hospital, Eindhoven,
The Netherlands*

Correspondence to:
Dr E. J. Th. Rutgers,
The Netherlands Cancer Institute
(Antoni van Leeuwenhoek Huis),
Plesmanlaan 121, 1066 CX
Amsterdam, The Netherlands

After treatment with curative intent of a primary breast cancer many patients are followed by regular out-patient visits, consisting of physical examination, routine laboratory testing and routine radiological and radionuclide examination. The main objectives of such follow-up are to detect as early as possible locoregional as well as distant recurrence or a second primary in the other breast. The investigations used in the routine follow-up of breast cancer patients are: radiograph of the chest, bone-scan, liver function tests and carcinoembryonic antigen[1]. However, although there has been considerable discussion about the usefulness of these tests in detecting breast cancer recurrence[2–7], there has been little discussion about the yield of the investigations in the follow-up of breast cancer. Are these routine investigations able to detect an asymptomatic—early—recurrence in a significant percentage of patients and how great is the number of investigations needed to obtain this result? The main question is whether the detection of an asymptomatic recurrence is beneficial to the patient.

An analysis of data obtained from a fixed follow-up schedule, consisting of routine chest and pelvic radiographs and laboratory tests, carried out for 416 patients over a period of 13 years, has been made in an attempt to answer these questions.

Patients and methods

The present study includes all patients treated with curative intent for breast cancer from 1970 to 1981 in the St. Joseph Hospital in Eindhoven In 467 patients breast cancer was diagnosed, 33 patients had distant metastasis at first diagnosis (stage IV) and 18 were lost from follow-up or insufficient data were available The remaining 416 patients were mainly treated by radical (before mid-1976) or modified radical (after mid-1976) mastectomy with radiotherapy when indicated After treatment patients were seen in the out-patient clinic every 3 months in the first 2 years, every 6 months up to 5 years, and annually thereafter. Besides physical examination and history, a radiograph of the chest and pelvis was made routinely at each visit and alkaline phosphatase γ-glutamyl transpeptidase, calcium, erythrocyte sedimentation rate and carcinoembryonic antigen (after 1978) were checked. Bone-scanning, liver imaging or mammography were performed only when indicated

Patients were followed for periods of up to 13·5 years. The cumulative follow-up period was 23 500 months, an average of 56 months per patient, most follow-up examinations and controls were carried out by surgeons Of the patients 89 per cent were followed according to the schedule. A specially designed follow-up form was used for the documentation of the results of history, physical examination and routine investigations at each follow-up visit.

The end points of the registration of follow-up data were. the last follow-up visit, the diagnosis of distant recurrence, or death unrelated to breast cancer

After the detection of distant recurrence, the time to the last follow-up visit and the time to death were registered.

The number of visits and routine investigations are listed in *Table 1* The treatment of distant recurrence was diverse and depended on localization and spread of the disease, the menopausal status of the patient and the oestrogen-receptor content of the tumour.

The most important treatment modalities were radiotherapy, chemotherapy, ovariectomy, tamoxifen or oestrogens (ethinylestradiol).

Results

Distant recurrence was found in 148 patients (36 per cent) and locoregional recurrence in 46 (11 per cent). Seventeen patients (4 per cent) developed a second primary cancer in the other breast.

The sites of the distant recurrences are listed in *Table 2* At the time of first diagnosis of distant recurrence 114 patients had related symptoms and, because of these symptoms, 77 patients

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had visited the out-patient clinic before the next scheduled visit. In other words, 34 patients had asymptomatic metastases which were discovered by routine investigation *Table 3* shows the means of discovery and the sites of these asymptomatic metastases.

At first diagnosis, 48 per cent of symptomatic patients had metastases at more than one site, against 21 per cent of asymptomatic patients (χ^2 test, $P<0\cdot05$) Survival after first diagnosis of distant recurrence was significantly longer for asymptomatic patients (see *Figure 1*). Of symptomatic patients, 70 per cent had axillary metastases at the time of primary treatment as against 53 per cent of the asymptomatic patients (χ^2 test, $P<0\cdot05$). *Figure 2* shows that the disease-free interval is the same for both asymptomatic and symptomatic patients.

Nine patients had their first detected metastases only in the lung, six of which initially seemed to be solitary. Five patients had progressive disease within 5 months. In one patient a wait-and-see policy was advised because of the lack of symptoms: 2·5 years later she died of the sequelae of progressive local tumour growth. Judged retrospectively, this patient might have benefited from a metastasectomy. None of the six patients with liver metastases as the only initial recurrence was considered to have solitary metastasis, neither were they regarded, retrospectively, to be resectable.

A locoregional recurrence was found during the follow-up period in 46 patients (11 per cent); in 42 patients this recurrence was found during a scheduled visit and 37 patients had not previously noticed this recurrence.

Seventeen patients developed a carcinoma in the other breast. Despite the regular physical examination only six second tumours were discovered at an early stage (<2 cm). The chance of finding a second primary breast cancer in this series is about 8·7 per 1000 follow-up years (17 in a total of 1958 years). The age-specific incidence of breast cancer in women over 30 years old in the Netherlands is 204 per 100 000 women per year (2·04 per 1000) The expected number of second breast cancers in a cumulative follow-up period of 1000 years is 2·04. The observed number of second breast cancers is 8·7; the observed.expected ratio is 4·2. Therefore in our population there is a fourfold increase in the risk of developing a second primary breast cancer.

Table 1 *The number of out-patient visits and routine investigations in 416 patients over a follow-up period of 13·5 years*

Investigation	*n*
Total out-patient visits	4533
Radiograph of the chest	4116
Radiograph of the pelvis	3889
Erythrocyte sedimentation rate	4153
Alkaline phosphatase	4101
γ-Glutamyl transpeptidase	3552
Calcium	3602
Carcinoembryonic antigen (after 1978)	1506

Table 2 *Site of distant recurrence at first diagnosis in 148 patients*

Site of recurrence	Only affected site	In combination with other sites	Total
Bone	51 (34)	41 (28)	92 (62)
Lung	9 (6)	29 (20)	38 (26)
Liver	6 (4)	26 (18)	32 (22)
Pleura	8 (5)	18 (12)	26 (18)
Brain	5 (3)	6 (4)	11 (7)
Ovary	2 (1)	9 (6)	11 (7)
Other	5 (3)	9 (6)	14 (9)

The total number of cases exceeds the number of 148 patients because in many patients metastases were diagnosed at more than one site These patients are included twice Values in parentheses are percentages calculated from the total number of patients

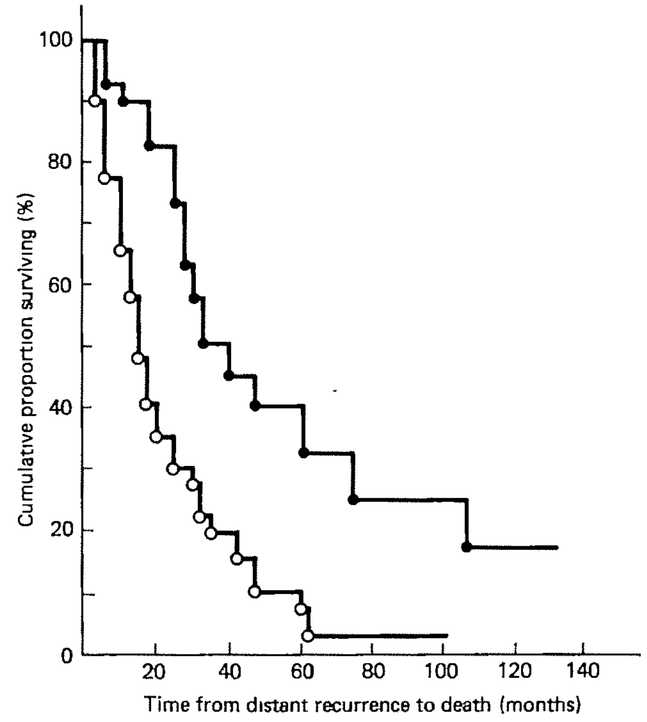

Figure 1 *Survival of patients according to symptoms from first diagnosis of distant recurrence. The difference in survival between the 114 symptomatic (○) and 34 asymptomatic (●) patients is significant (P<0·0001, Lee–Desu statistic[18])*

Table 3 *The number and type of routine investigations which revealed asymptomatic distant recurrence in 34 patients*

Site of asymptomatic recurrence	Radiograph			Laboratory tests	Total
	Chest	Pelvis	Chest + pelvis		
Bone	2	5	3	4	14
Lung/pleura	9	—	—	—	9
Bone/lung/pleura	3	—	1	—	4
Bone/liver	—	—	—	1	1
Bone/other sites	—	—	—	1	1
Liver	—	—	—	3	3
Lung/ovary*	1	—	—	—	1
Local/ovary*	—	—	—	—	1
Total	15	5	4	9	34

* After the detection of the asymptomatic lung and local recurrence these two patients underwent an ovariectomy In the ovaries of both patients an unexpected metastatic tumour was found. † This patient had asymptomatic distant recurrence in the ovary which was not discovered by routine investigations but which was discovered in the therapeutically removed ovary

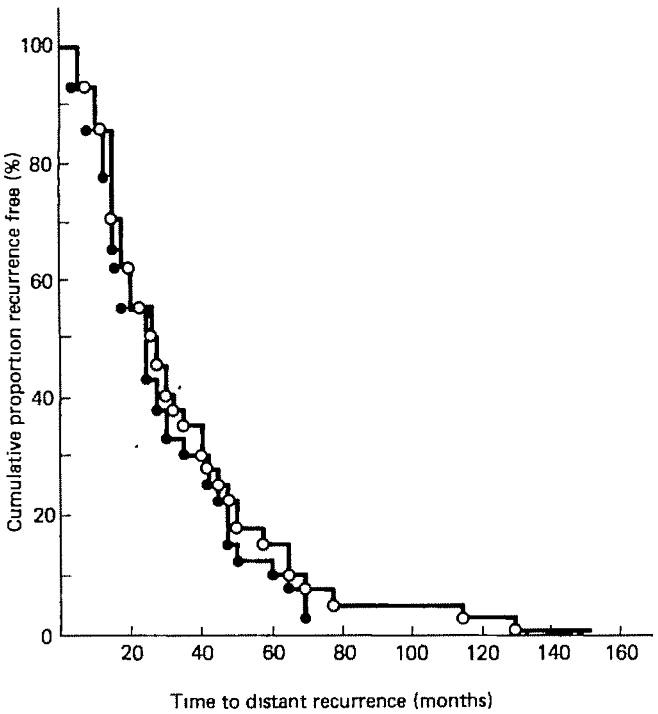

Figure 2 *Distant recurrence-free interval according to recurrence-related symptoms. Screening for metastases did not reduce the lead time in the diagnosis of asymptomatic metastases for there is no difference in the time to distant recurrence between 114 symptomatic* (○) *and 34 asymptomatic* (●) *patients* (*Lee–Desu statistic*[18])

Discussion

In order to detect a relatively small number of asymptomatic metastases (23 per cent of the total), it was necessary to carry out a large number of routine investigations: 4116 chest radiographs to discover 19 pulmonary, pleural or bone metastases; 3889 pelvic radiographs to discover nine bone metastases and about 17000 laboratory tests to detect six bone and four liver recurrences. This degree of investment is only justifiable if the patients can expect to benefit from the early detection of asymptomatic and distant recurrence.

What are, in theory, the most important benefits to be expected from early detection?

Firstly, a smaller tumour burden might give a better response to systemic therapy with a longer survival and/or symptom-free interval. Secondly, routine testing might provide an opportunity to detect solitary liver or pulmonary metastases at a stage when they can be cured by surgical excision.

However, one can raise several objections against these hypothetical advantages. The asymptomatic recurrence, as well as the symptomatic recurrence, represents a macroscopic tumour mass Both contain more than 10^{10} tumour cells. According to the theory of Goldie and Coldman[8] and Goldie[9], these tumour masses are supposed to contain a sufficiently large number of resistant tumour cells to ensure persistence of the tumour localization after endocrine therapy or chemotherapy In other words, in macroscopic metastatic breast cancer cure is not to be expected. In addition, as the difference between the number of resistant cells in asymptomatic or in symptomatic patients is small, no important survival benefit is to be expected by treating asymptomatic breast cancer metastases. There are some reports supporting this last statement: Zwaveling *et al.*[10], Brøyn and Frøyen[11], as well as Hietanen[12], were not able to detect any survival benefit from treating asymptomatic metastases. We did find a longer survival after detection of metastases in asymptomatic patients, but it was probably not due to better treatment response in the asymptomatic patients but to patient selection: most symptomatic patients had more extensive disease at the time of diagnosis of the recurrence and there had been a higher incidence of axillary metastasis in the symptomatic patients at the time of primary treatment. From these data one can speculate that patients whose recurrences presented with symptoms were suffering from a more vigorous type of breast cancer. In general, it is disputable whether systemic chemotherapy improves survival in metastatic breast cancer patients to the degree that it outweighs the discomfort caused by the treatment[13–15].

The hypothetical advantage of prolonging the symptom-free interval by treating asymptomatic metastases has to be weighed against the real disadvantage of shortening the subjective disease-free interval by detecting and treating asymptomatic recurrences The patient feels well but has been made aware of the fact that the disease has spread. Moreover she may receive a therapy which will make her sick. The treatment of metastatic breast cancer is nearly always palliative, with excellent results in only a small percentage of cases. Therefore, one should start this treatment only when clearly indicated

The chance of finding a curable, truly solitary, pulmonary or liver recurrence is extremely small. In our series there was probably an indication for a resection of a lung metastasis in only one patient and in none of the patients with liver metastases. Vincent *et al* [16] reported two patients, out of a group of 1000 patients with breast cancer metastases, who underwent a pulmonary metastasectomy resulting in a long survival

For this reason we feel that it is unnecessary to make an intensive and onerous search for asymptomatic breast cancer metastases. And thus, in our opinion, there is no need for routine biochemical and radiographic investigations in the follow-up of breast cancer patients. That regular physical examination is important has been shown by the fact that the great majority of local recurrences were detected during routine control visits Early detection and treatment of a local recurrence is able to prevent distressing local problems. As most distant recurrences are heralded by symptoms[17], it is important to see the patient regularly to give her the opportunity of bringing forward even minor complaints.

Because of the increased risk of a second primary tumour, surveillance of the other breast by regular physical examination and mammography is mandatory. There is a real chance for cure of a second primary breast cancer detected at an early stage. The optimal interval for mammography in this high-risk group of patients is not defined This interval will have to depend on supplementary risk factors, such as age, histological features of the primary tumour (lobular carcinoma) and family history. Probably, performing an annual mammography is a satisfactory compromise for most patients, although it is not clear whether such screening will improve survival for breast cancer treated patients.

In addition to these purely medical considerations, the regular routine check-up gives the patient the opportunity to present psychological problems, which are so frequent in breast cancer patients. The routine check-up is able to reassure the patient that 'all is well' and, last but not least, it gives the doctor the opportunity of evaluating the results of the breast cancer treatment as performed in the clinic.

In conclusion, follow-up after treatment for primary breast cancer is useful: local and/or regional recurrence, or a second primary breast cancer can be detected at an early stage. Signs and symptoms of possible distant recurrence will come to light and by further investigations any suspicion will be confirmed or excluded The only routine steps required are taking the history, physical examination, and an annual mammography, on a fixed time schedule. Carrying out other investigations is a costly way of detecting a few asymptomatic metastases for which no therapeutic advantages can be expected.

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Prior renal transplantation does not facilitate subsequent canine islet allograft survival

A. J. Guy, S. M. Griffin, D. Alderson and J. R. Farndon

Department of Surgery,
The Medical School, Framlington
Place, University of Newcastle
upon Tyne, Newcastle upon Tyne
NE2 4HH, UK
Correspondence to: Mr A. J Guy

Successful islet allografts can be established in rats bearing long surviving renal allografts, without additional immunosuppression, when kidney and islet donor animals are of the same strain. The applicability of such a scheme to clinical practice has been investigated in a large animal model of diabetes: the pancreatectomized dog. Eight dogs with previously established renal allografts and immunosuppressed with cyclosporin A received islet allografts from their respective original kidney donors. The median islet graft functional survival was only 10·5 days, significantly less than for six similarly immunosuppressed dogs receiving islet allografts alone (48·5 days, $P<0\cdot05$). Three of the sequentially transplanted dogs had had no renal graft rejection episodes before islet transplantation, yet their islet grafts were all rejected within 19 days. In the pancreatectomized dog, prior donor specific renal transplantation has an adverse effect upon subsequent islet graft survival.

Keywords: Diabetes, cyclosporin, islet transplantation, renal transplantation, immune tolerance

Prolonged islet allograft function has been difficult to achieve in most experimental models of diabetes mellitus when using conventional immunosuppression, but it must be demonstrated before safe clinical islet transplantation can proceed. Rats with established renal allografts, subsequently made diabetic with streptozotocin, regularly accepted islet grafts from the original kidney donor strain with prolonged reversal of diabetes and without the need for further immunosuppression[1]. These findings were independent of the strain combination and the site of islet graft placement[2]. If such a scheme were successful in a large animal model of diabetes it might have clinical application. Renal impairment or failure will develop in up to 40 per cent of insulin-dependent diabetic patients within 30 years of diagnosis[3] and many of these patients could be considered for renal transplantation. At the time of renal transplantation in a patient with diabetes, islets could be harvested from the same kidney donor and cryopreserved for transplantation once the renal graft was well established. Not only might the diabetic state be successfully reversed, but the transplanted kidney might be protected against the development of diabetic nephropathy[4]. The aim of this study was to investigate the feasibility of such a scheme using the pancreatectomized dog as a model of human insulin-dependent diabetes mellitus[5]. Islet graft survival after sequential renal and islet allotransplantation, with cyclosporin A immunosuppression, was compared with islet graft survival after similarly immunosuppressed islet allotransplantation alone

Materials and methods

Animals

Healthy young adult beagle dogs were used with weights ranging from 10·5 to 21·7 kg. They received a standard kennel diet supplemented with Pancrex Granule Fines (Paines and Byrne Ltd., UK) after pancreatectomy.

Experimental groups

Group 1: islet allograft ($n=6$)
Group 2: islet allograft + cyclosporin A ($n=6$)
Group 3: sequential renal then islet allograft + cyclosporin A ($n=16$)

All transplants were performed between unrelated animals (either from different colonies or unrelated for at least three or four generations according to breeders' records).

Animals in groups 1 and 2 underwent total pancreatectomy 1 week before islet allotransplantation, fasting normoglycaemia being maintained in the interim with subcutaneous insulin injections In group 3 renal transplants were established between 11½ and 15 weeks before islet transplantation from the original kidney donors. In group 3 recipients, pancreatectomy was performed at the same time as the islet transplant

Surgery

Animals were premedicated with atropine (300 μg) and acepromazine (1·5 mg). Anaesthesia was induced with thiopentone (10 mg kg^{-1}) and maintained with halothane, nitrous oxide and oxygen Cefuroxime (500 mg) was given at the start of surgery. Hartmann's solution, 100 ml h^{-1}, was given intravenously during surgery. Postoperative analgesia was ensured with buprenorphine (100 μg).

Total pancreatectomy was performed, preserving the pancreaticoduodenal vessels, and the excised gland was immediately placed in iced Hanks' balanced salt solution (HBSS)

For renal transplantation the left kidney was excised and flushed with iced heparinized kidney perfusion solution (Travenol, Thetford, UK). It was transplanted to the right iliac fossa of the bilaterally nephrectomized recipient animal and anastomosed end-to-end with the iliac artery and end-to-side with the iliac vein. An onlay ureteroneocystostomy was performed[6]. Fifty millilitres of 10 per cent mannitol solution was given intravenously during the anastomosis Kidney donor animals recovered from unilateral nephrectomy and subsequently acted as islet donors for their respective recipient animals.

Islet graft preparation and transplantation

Retrograde ductal perfusion (20 ml min^{-1}) of a 0·05 per cent collagenase solution (Sigma type X, activity 2400 units mg^{-1}) at 37°C for 18–24 min was followed by mechanical dissociation and serial sieving (425 μm pore size) in iced HBSS Graft fragments were separated by refrigerated centrifugation, final graft volume was measured and they were resuspended in iced HBSS with aprotinin (2×10^5 KIU litre^{-1}) for implantation. The presence of isolated islets in the graft was confirmed by immediate microscopy using a green filter[7]. Prepared islet grafts were implanted into the splenic pulp of recipient animals during temporary occlusion of the splenic vascular pedicle

Immunosuppression

Group 2 animals received cyclosporin A, 20 mg kg^{-1} day^{-1}, by intramuscular injection starting 5 days before islet transplantation After transplantation the dose was adjusted, attempting to maintain the plasma cyclosporin A concentration above 400 ng ml^{-1}. Cyclosporin A was given by intramuscular injection because of uncertainties about the adequacy of its gastrointestinal absorption after pancreatectomy, despite apparently adequate exocrine supplementation[8,9].

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Group 3 animals received cyclosporin A, 20 mg kg^{-1} day^{-1}, orally (the pancreas being entirely normal at this stage of the experiment), starting the day before renal transplantation. Following renal transplantation episodes of presumed renal rejection (diagnosed by a rapid rise in plasma creatinine concentration of $>35\,\mu$mol litre^{-1} day^{-1}) were treated with intravenous methylprednisolone, 60–120 mg, for 3 days. To ensure comparability with group 2, intramuscular cyclosporin A was started 5 days before sequential islet transplantation and oral cyclosporin A stopped 2 days beforehand Subsequent dose adjustment was as for group 2

Assessment

Fasting plasma glucose and insulin concentrations were measured after islet transplantation on days 1–14, 17, 21 and weekly thereafter. Plasma creatinine concentrations were measured on days 1–14 after renal transplantation and weekly thereafter. After the sequential islet transplant, creatinine was measured on the same days as glucose and insulin.

Plasma cyclosporin A concentrations were measured on days 0, 2, 4, 7, 10, 14 after islet transplantation and weekly thereafter and on the day of renal transplantation and then weekly Blood samples were incubated at 37°C for 30 min before plasma separation and analysis by polyclonal radioimmunoassay (Cyclosporin RIA-Kit, Sandoz Ltd , Leeds, UK).

Dogs ($n=16$) acting as kidney and islet donors for group 3 animals had their plasma creatinine concentrations measured before and after initial unilateral nephrectomy.

Criteria for experimental termination

The experiment was terminated if animals survived for 6 months after islet transplantation, if the fasting plasma glucose concentration was >25 mmol litre^{-1}, if animals lost more than 25 per cent of their preoperative body weight or if irreversible renal failure occurred.

Statistical analysis

Data are expressed as median and range The Mann–Whitney *U* test has been used for all comparisons

Results

In group 3, eight dogs died following initial renal transplantation: on day 7 (renal artery thrombosis), on days 6 and 8 (intussusception), and on days 36, 51, 51, 68, 70 (renal rejection with terminal creatinine concentrations of 627, 788, 666, 669, 867 μmol litre^{-1} respectively). Eight dogs survived to undergo sequential islet transplantation.

Islet graft function

There were no differences between the three groups in final pancreatic microfragment graft volume (or graft volume as a percentage of donor pancreas weight).

Days of islet graft function (maintenance of normoglycaemia) and the total number of days survived after islet transplantation in the three groups are shown in *Table 1*. Non-immunosuppressed allografts were rapidly rejected. Cyclosporin A immunosuppression allowed significant prolongation of islet allograft function (group 2 *versus* group 1, $P<0·005$). Sequential islet grafts functioned for a significantly shorter time than islet allografts (group 3 *versus* group 2, $P<0·05$) and animal survival was similarly reduced (group 3 *versus* group 2, $P=0·01$). Animal survival for group 3 was no different than for group 1.

Table 1 *Days of islet graft function and total animal survival following islet allotransplantation in three groups*

	Graft function (days)	Total survival (days)
Group 1	2, 3, 4, 4, 5, 5	6, 7, 10, 10, 16, 16
Group 2	22, 35, 41, 56, 64, >182	27, 47, 48, 71, 79, >182
Group 3	4, 4, 7, 9, 12, 14, 18, 73	6, 9, 11, 13, 13, 20, 24, 73
Group comparison		
1 *versus* 2.	$P<0·005$	$P<0·005$
1 *versus* 3	$P<0·05$	n s
2 *versus* 3:	$P<0·05$	$P=0·01$

n.s., Not significant· comparisons were by the Mann–Whitney *U* test

Table 2 *Comparison of plasma creatinine and cyclosporin A concentrations on the day of islet allotransplantation between groups 2 and 3*

	Creatinine (μmol litre^{-1})	Cyclosporin A (ng ml^{-1})
Group 2	49, 59, 76, 76, 76, 79	100, 267, 304, 389, 599, 1093
Group 3	68, 75, 77, 83, 152, 157, 205, 311	68, 82, 306, 393, 782, 983, 1180, 2395
Group comparison		
2 *versus* 3.	n.s.	n s.

n s., Not significant; comparison by the Mann–Whitney *U* test

Table 3 *Terminal plasma creatinine and glucose concentrations for group 3 animals following sequential islet transplantation*

Creatinine at sequential transplantation (μmol litre^{-1})	Creatinine at termination (μmol litre^{-1})	Glucose at termination (mmol litre^{-1})
Subgroup (a)		
75	216	35·7
77	114	26·6
83	166	27·3
Subgroup (b)		
152	158	23·0
157	131	27·9
205	591	15·8
311	781	42·0
Subgroup (c)		
68	236	4·2

(a), No episodes of previous renal allograft rejection, (b), multiple previous episodes of reversible renal rejection; (c), one episode of renal rejection

Cyclosporin A and creatinine

Plasma cyclosporin A and creatinine concentrations for groups 2 and 3 on the day of islet transplantation are compared in *Table 2*. There were no significant differences in cyclosporin A levels either then or during the subsequent post-islet transplant period. Group 3 animals had a higher median plasma creatinine concentration on the day of islet transplantation, although this did not reach statistical significance ($P=0·06$).

Individual group 3 results

The eight dogs in group 3 which received sequential islet grafts had marked differences in renal function and are considered in three subgroups. The terminal plasma glucose and creatinine concentrations for these animals are shown in *Table 3*.

No episodes of previous renal allograft rejection. Three dogs never experienced renal rejection before sequential islet transplantation (creatinine concentrations at islet transplantation 75, 77, 83 μmol litre^{-1}) yet their islet grafts functioned for only 7, 18 and 9 days respectively. All these dogs demonstrated mild renal impairment following sequential islet transplantation (*Table 3*). An example of the post-islet graft changes in plasma glucose, insulin and creatinine concentrations for one of these animals is illustrated in *Figure 1*. In this animal loss of glycaemic control was preceded by a fall in the plasma insulin concentration. The terminal rise in creatinine may have been due to either concomitant acute renal rejection or dehydration accompanying severe diabetes and glycosuria.

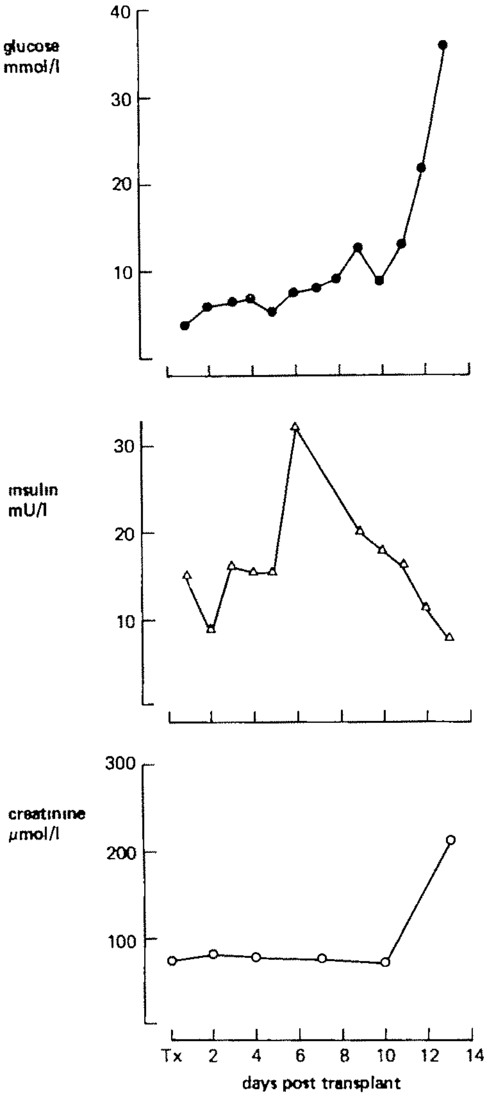

Figure 1 *Post-islet transplant changes in glucose (●), insulin (△), and creatinine (○) concentrations for one animal with no episodes of renal rejection before sequential islet transplantation*

Multiple previous episodes of reversible renal allograft rejection. Four dogs had experienced multiple episodes of renal rejection (median 3, range 2–4) including one within the 3 weeks preceding the islet graft (creatinine concentrations at islet transplantation 152, 157, 205, 311 μmol litre^{-1}). Their islet grafts functioned for 4, 14, 4 and 12 days respectively, with associated marked deterioration in renal function occurring in two animals (*Table 3*).

One episode of renal rejection. One dog had an episode of renal rejection 2 weeks after initial renal transplantation (creatinine rose from 72 μmol litre^{-1} to 199 μmol litre^{-1} in 2 days) The islet graft 10 weeks later maintained fasting normoglycaemia until the experiment was terminated because of severe weight loss and moderate renal impairment, 73 days after islet transplantation.

Deteriorating renal function occurred in most animals as a terminal event (*Figure 1*, *Table 3*). It was not possible to discern whether such deterioration in renal function was coincidental, occurred as a result of the islet transplant, or was a result of the diabetes which accompanied islet graft failure. In one animal renal rejection after sequential islet transplantation was reversed with a 3-day course of methylprednisolone, but islet graft failure followed. Steroid treatment was not given for presumed renal rejection following the islet graft in subsequent animals.

Effect of unilateral nephrectomy in donor animals

The plasma creatinine concentration rose significantly ($P < 0.001$) from 73·5 μmol litre^{-1} (range 57–101 μmol litre^{-1}) to 88 μmol litre^{-1} (range 76–104 μmol litre^{-1}) after unilateral nephrectomy.

Discussion

In this model of diabetes, prior donor specific renal transplantation has an adverse effect upon subsequent islet graft survival. The only significant difference between the two immunosuppressed groups at the time of islet transplantation was the presence of a prior renal allograft. The slightly higher creatinine level in group 3 at the time of islet transplantation, although not significantly different from group 2, was unavoidable; these animals were surviving on their transplanted kidney which, in many instances, had undergone episodes of rejection. It should be noted that in the animals acting as kidney donors unilateral nephrectomy resulted in a slight, but highly significant, rise in the plasma creatinine concentration Bolus steroid treatment reversed most episodes of acute renal rejection, but the plasma creatinine concentration rarely returned to its previous level. The diagnosis of rejection in these animals was based on clinical and biochemical findings only, supported by the response to steroids Other potential causes of a rapid deterioration in renal function, such as renal artery or vein thrombosis, would not have been amenable to treatment in these animal experiments Cyclosporin A nephrotoxicity has not been noted in dogs receiving considerably higher doses of cyclosporin A than were used in the present study[10,11]. Significant renal impairment would be more likely to have had an immunosuppressive effect than to have promoted islet graft rejection. Such impairment, as seen in this study, is unlikely to have influenced cyclosporin A pharmacokinetics. In dogs, as in man, urinary excretion is an unimportant route of cyclosporin A elimination[12].

The final eight dogs in group 3 were, to some extent, a selected group, being those which had survived for 3 months with renal allografts. The three animals which had never had episodes of renal rejection before sequential islet transplantation may have been particularly tolerant of their renal graft and rapid islet graft failure in these animals was unexpected. It was in these animals that prolonged islet graft function might have been anticipated. Sequential islet transplantation at a time of unstable renal function is clearly inappropriate, as shown by the outcome of those animals that had had multiple renal rejection episodes before islet transplantation. The mechanism of earlier islet graft failure following sequential islet transplantation remains unclear. In the cases of rapid islet graft rejection, recipient animals may have become sensitized to donor antigens with the second antigenic challenge (islets) resulting in islet, and in some cases renal, rejection.

Two areas require consideration before the results of these large-animal experiments are extrapolated to man.

The islet grafts prepared in the present experiments were relatively impure. Accurate assessments of islet graft purity were not performed, but we have previously reported a median graft insulin content of 26 per cent when using a similar method of graft preparation[13]. Quantification of islet yield by counting, with calculation of graft islet volume[14], is probably more accurate, but the limitations and difficulty of this technique with an impure islet graft are obvious. Gotoh *et al.*[15] reported unrefined rodent islet grafts to be rejected more quickly than pure preparations and suggested that contaminating tissues such as vascular or ductal fragments were a major stimulus to induction of acute rejection. It is conceivable, therefore, that a pure islet graft preparation might meet with a more favourable outcome after allotransplantation in both dog and man It has also been reported, however, that there is no difference between the rejection of pure and impure islet grafts in rodents[16].

The potential effects of islet cryopreservation, required in clinical practice, need to be considered. In the present experiments cryopreservation was not used, as the design of the study allowed islets to be maintained *in vivo* Techniques of canine islet graft cryopreservation do not yet allow reproducible and successful graft function following autotransplantation[5], and introduction of such a potential source of islet damage and variable function was not appropriate in these preliminary experiments. Cryopreservation is a potential method of islet immunoalteration and prolongation of rat to mouse islet xenograft survival by cryopreservation has recently been claimed[17]. Cryopreservation has not altered fresh or cultured human islet antigenic expression[18] and it is, therefore, unlikely that it would alter the outcome of human islet transplantation.

The marked disparity in the results of sequential renal and islet transplant experiments in rats[1,2] and these results for dogs are probably due to basic immunological differences between the two species. In the rat a short course of cyclosporin A treatment allows the establishment and long-term function of a renal transplant—a state of immune tolerance. In dogs a short course of cyclosporin A has allowed only slight prolongation of renal allograft survival and continued immunosuppressive treatment is required to allow long-term graft function[19]. Dogs are not tolerant of their renal allografts and sensitization to donor antigens may ensue, as suggested by the rapid failure of many of the sequential islet grafts in this study. Further work is required before attempting to adopt the single donor sequential renal and islet transplant scheme to clinical practice.

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Attitudes of operating theatre staff to inoculation-risk cases

C. D. Johnson, R. Evans, D. C. Shanson and C. Wastell

Departments of Surgery and Medical Microbiology, St Stephen's Hospital, London SW10 9TH, UK
Correspondence to:
Mr C D. Johnson, Department of Surgery, 'F' Level, Southampton General Hospital, Southampton, UK

In a 12-month period, 177 patients at risk of infection with human immunodeficiency virus (HIV) or hepatitis B were operated on. Sixty-nine had HIV antibodies. The procedures used to identify these patients and minimize the risk of infection of hospital staff in the operating department are described. All staff working in the operating department were surveyed to determine their caseload, feelings of anxiety, and the incidence of high-risk exposure to infection. Anxiety was not related to workload, but was more common in those who had high-risk exposure. All members of staff who sustained a needlestick injury were tested for HIV antibodies at intervals after injury; 33 also volunteered to be tested in a screening session 3 months after the study period. None had HIV antibodies, suggesting that the risk of acquiring HIV infection in the operating department is low.

Keywords: Human immunodeficiency virus, hepatitis B, nosocomial infections, surgical technique

Surgeons, anaesthetists and theatre staff have faced the risk of inoculation with infective agents since surgery began. The present epidemic of human immunodeficiency virus (HIV) infections has increased awareness of this risk. Medical personnel exposed to blood, blood products and body fluids are also at risk of contracting hepatitis B, which is more readily transmissible than HIV infection[1] and is also found at increased incidence in the homosexual population.

Male patients with anorectal complaints constitute 10 per cent of new referrals to our general surgical out-patient clinic. In 1985, half of these were homosexual, of whom 38 per cent had evidence of one or other of these transmissible infections[2]. The catchment area of this hospital includes a large homosexual community. We see many patients who are potentially infected with hepatitis B, HIV and other sexually transmissible disorders

As a consequence of our catchment population, we operate on many patients who fall into an 'inoculation risk' group. Stringent precautions are taken to prevent infection of staff by inoculation with blood or other body fluids from these patients Our precautions are based on the Department of Health and Social Security (DHSS) guidelines for prevention of infection of hospital staff in general wards and in the operating theatre, for both hepatitis B[3] and HIV[4]. These guidelines should be adequate to protect operating theatre personnel if they are adhered to rigorously.

However, the implementation of the procedures may in itself increase the anxiety of the medical and nursing staff who are dealing with these patients. This paper examines our experience and its effects on the attitudes of operating department staff to their work with such patients.

Patients and methods

The following groups were deemed to be patients who posed an inoculation risk for HIV and hepatitis B homosexuals and bisexuals, all drug abusers, haemophiliacs, patients known to be HIV antibody or hepatitis B antigen positive, all cases of infective jaundice; patients from high-risk areas, such as central Africa, Haiti, certain parts of the USA, including visitors to those areas who have received blood transfusions there; any institutionalized person, and sexual partners and children of all these persons The number of such patients who were operated on in a 12-month period was recorded.

Patients at risk of these infections were offered hepatitis B and HIV antibody tests. Counselling was given and informed consent was obtained before testing for HIV antibodies All patients at risk were designated 'inoculation risk' with the exception of those whose risk factor was previous jaundice and who were known to be hepatitis B antigen negative. Inoculation risk cases were managed in the operating theatre in accordance with our hospital procedure, which is based on the DHSS guidelines[3,4] Copies of our detailed procedure are available from one of the authors (D.J.S.) At this hospital, we have designated a 'dirty' operating theatre. All inoculation risk cases and other infected cases are operated on in this theatre.

At the end of the study period, a survey was carried out of all personnel working in the operating theatres who might have been exposed to hepatitis B and HIV infections. These were the surgeons, anaesthetists, scrub nurses, anaesthetic nurses and operating department assistants. The survey questionnaire (*Table 1*) was designed by one of us (C.D.J.) to assess the degree of involvement of each member of staff in inoculation risk cases and to gauge their reaction to this workload The survey questionnaire was sent to each member of staff who was working in the operating theatre. Confidentiality was ensured by the following procedure. A numbered envelope was sent with each questionnaire, for its return The numbers were checked against a reference list, and reminders were sent as necessary When all questionnaires had been received, the reference list was destroyed, and the envelopes were opened No personal identification was possible from the completed questionnaires. The survey results were then presented at a meeting held in working hours in the operating department All members of staff present were invited to provide a blood sample to determine the prevalence of hepatitis B and HIV infections in the department Those who agreed had blood taken at once.

Results

In all, 5986 patients were operated on during the study period, of whom 177 were designated as 'inoculation risk'. Eight patients were hepatitis B risks only, and 169 were at risk for both hepatitis B and HIV, of whom 69 (41 per cent) had HIV antibodies. The remainder were equally divided between those with negative antibody tests, and those who refused testing. General surgeons treated 153 patients. The remainder were treated by various departments: gynaecology (three), orthopaedic surgery (two), dental surgery (thirteen), urology (five) and accident surgery (one).

Seventy-three questionnaires were sent to members of staff. Replies were received from 24 of 32 surgeons, 10 of 12 anaesthetists, 12 of 14 scrub nurses, and 12 of 15 anaesthetic nurses and operating department assistants (*Table 1*). Failure to reply after two requests was usually because the member of staff had left for other employment.

The relationships between exposure and anxiety were examined. There was no correlation between the self-reported caseload and anxiety, expressed as a reply of 'very anxious' or

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Table 1 *Responses of operating department staff to the questionnaire*

1. How long have you worked at St Stephen's?

Surgeons ($n=24$)	15 months (2 months–15 years)
Anaesthetists ($n=10$)	8·5 years (2 months–22 years)
Scrub nurses ($n=12$)	11 months (2 months–4·5 years)
AN/ODA ($n=12$)	4 years (4 months–12 years)

(median and range values given)

2 How often do you personally deal with inoculation risk cases?

	≥3 per week	1 or 2 per week	1 or 2 per month	<1 per month
Surgeons	1	11	10	2
Anaesthetists	3	6		
Scrub nurses		10	1	1
AN/ODA	2	10		

3 Have you had a high-risk exposure* to hepatitis B or HIV infection at work?

Surgeons	9 (2 needlestick, 1 HIV, 2 hepatitis B)
Anaesthetists	5
Scrub nurses	0
AN/ODA	3 (2 needlestick, 1 HIV, 1 hepatitis B)

(*Needlestick injury, blood in eye, blood on skin)

4. How do you feel about dealing with inoculation risk cases?

	Very anxious	Uneasy	Not worried	Interested
Surgeons	2	15	5	3
Anaesthetists		10		1
Theatre nurses		8	4	
AN/ODA	4	4	3	4

(One surgeon and one anaesthetist felt both uneasy and interested One AN/ODA felt very anxious and interested; two AN/ODA were not anxious and interested)

5 Would you be happy to deal with: more cases, the same number or fewer cases?

	More cases	Same number	Fewer cases
Surgeons	4	8	12
Anaesthetists		1	9
Theatre nurses		2	9
AN/ODA		3	9

6. When looking for your next job, will the number of inoculation risk cases you would deal with be of no importance, of minor importance, affect your decision to take the job?

	No importance	Minor importance	Affect decision	No reply
Surgeons	6	11	2	5
Anaesthetists	3	4		3
Scrub nurses	1	7	4	
AN/ODA	3	3	6	

7. Does dealing with inoculation risk cases make you wish you worked somewhere else?

	Yes	No
Surgeons	7	15
Anaesthetists	3	7
Theatre nurses	3	9
AN/ODA	4	8

AN/ODA, recovery and anaesthetic nurses and operating department assistants

'uneasy' to question 4 Of 43 members of staff who dealt with one or more cases per week, 33 expressed anxiety, compared with nine of 13 who handled fewer than one case per week. In contrast, 32 of 43 members of staff with a reported caseload of one or more per week expressed a wish to do fewer cases, compared with five of 13 who dealt with fewer than one per week.

Anaesthetists uniformly expressed anxiety about handling inoculation risk cases, compared with 17 of 24 surgeons and 16 of 24 scrub nurses, anaesthetic nurses and operating department assistants. A history of high-risk exposure was associated with an increased expression of anxiety. Two surgeons who had sustained needlestick injuries were both uneasy, and two anaesthetic nurses or operating department assistants were both very anxious Of 17 staff who had had high-risk exposure (blood in the eye or on the skin, or a needlestick injury), 16 expressed anxiety, compared with 28 of 41 others Fourteen with high-risk exposure, compared with 25 of 41 without, expressed a wish to handle fewer cases. No member of staff who had a high-risk exposure has subsequently developed HIV antibodies.

Thirty-three members of staff (ten doctors and 23 nurses) provided a blood sample. All were tested for HIV antibodies and hepatitis B markers. All HIV tests were negative. Three nurses had hepatitis B core antibodies, indicating previous infection These individuals were all from the Indian subcontinent. No other member of staff showed evidence of hepatitis B infection.

Discussion

St. Stephen's Hospital serves a population with a large homosexual community. There is also a drug dependency unit in the hospital. In order to minimize the risk of nosocomial infection, the admitting doctor routinely asks a detailed sexual and drug history of all surgical patients. It is our experience that patients are usually willing to provide this information. Until one becomes used to it, such questions are frequently more embarrassing for the surgeon than for the patient. This policy identified 177 patients at risk of carrying hepatitis B or HIV in one calendar year. We feel that awareness of the possibility of HIV infection and specific enquiry to detect risk factors are major safeguards for the surgeon and the operating team.

We designated as inoculation risks all patients in groups at risk of HIV infection, irrespective of antibody tests. In contrast to those with hepatitis risk only, in whom a negative hepatitis B antigen test excludes infection, the absence of HIV antibodies cannot be taken as a guarantee of safety. In future, a reliable HIV antigen test that had been shown to correlate with HIV infection would enable us to exclude antigen-negative patients from the inoculation risk group.

The DHSS guidelines for handling inoculation risk patients in the operating department pose several constraints. For the operating team, the need to wear eye protection reduces visual fields. We find that transparent visors are more comfortable and less prone to condensation than goggles. We recommend that the surgeon wear two pairs of gloves while operating in the hope that this affords some protection against needlestick injuries. Most surgeons adapt quickly to wearing two pairs of gloves. For comfort, the second pair should be half a size larger. The recommendation to clean the theatre, and to allow it to stand empty for 1 h, effectively limits the number of inoculation risk cases to one per session. We have found it administratively easier to designate one theatre for all dirty and inoculation risk cases. No staff are allocated for this theatre: the surgical team transfers into the dirty theatre when necessary

It is for these reasons that we prefer to identify, by careful enquiry, patients at risk from HIV and hepatitis B infection and to take these extra precautions with those cases only. As others have pointed out[5], to apply these stringent additional precautions to every case would be inconvenient and expensive because of the increased use of disposable items, and it would greatly reduce surgical throughput. However, we have adopted the recent advice of the Royal College of Surgeons of England[6] to reduce the risk of needlestick injuries in all surgical procedures. Knives, needles and sharp instruments are not passed from hand to hand, but are laid in a dish and picked up by the recipient. Needles are held with instruments whenever possible.

It is arguable whether additional inoculation risk precautions should also be taken in all cases where a history is not available, for example when an emergency operation is done on an unconscious patient. We did not advise such a policy at the time of this study, but our previous experience of unwitting operations on hepatitis B carriers and the high prevalence of HIV in our catchment area have now led us to use full inoculation risk precautions in those circumstances.

The survey questionnaire was designed to determine how the staff perceived their inoculation risk workload, and its effect on them. This subjective assessment clearly has limitations. Workload was overestimated by the respondents, when compared with known numbers of cases and staffing levels. Subjective assessment of anxiety is probably only an approximation to the underlying level of anxiety, but is justified in this survey for three reasons: a simple questionnaire was used to encourage a high response rate; although self-reported feelings of anxiety were common they were likely to be an underestimate rather than an overestimate; and finally, we wished to establish people's perception of their situation, rather than some theoretically 'true' level of anxiety. The study showed no correlation between the self-reported rate of exposure, and feelings of unease or anxiety among department staff, although those with a high caseload were more likely to wish to perform fewer such cases. Therefore, the high incidence of reported anxiety in anaesthetists cannot be related only to their workload. Perhaps the nature of their work, with constant exposure to secretions, may contribute. Although a greater proportion of anaesthetists who replied were of consultant status than in other groups, the significance of this is doubtful because length of service in the hospital did not appear to have any relationship with expression of anxiety. Furthermore, all anaesthetists, junior and senior, were uneasy about inoculation risk cases.

The higher incidence of anxiety in those sustaining high-risk exposure to infection (needlestick injury, or blood spilt on the skin or in the eye) points to a need for counselling and education for these members of staff. If they can be reassured, then others may also worry less about potential risks.

It appears that HIV has a low infectivity in the hospital environment[1,7,8]. Nevertheless, it is worrying that we had so many high-risk exposures. Glove perforations and needlestick injuries are common[9,10], and their avoidance requires greater care in surgical technique and in the handling of used needles. Adequate protective clothing, including gloves for all personnel and surgical gowns with impervious sleeves, is essential. Our study confirms the low risk of these cases to theatre staff, despite the heavy workload. After 17 known high-risk exposures (with four needlestick injuries), there was no evidence of seroconversion from negative to positive antibody status for HIV, nor of infection with hepatitis B. The prevalence of HIV antibodies amongst medical and nursing staff who volunteered to be tested was zero, which also suggests that no member of staff was accidentally infected at work with this organism.

Although nine cases of occupational infection with HIV have been recorded in the literature, the risk is extremely low. In 1642 documented needlestick or blood splash exposures to HIV, there has been one seroconversion[8]. Three cases of seroconversion after surface exposure to blood all involved blood spilt on damaged skin or into the mouth, and two others were in women who provided long-term care at home for patients with AIDS[8]. Four nurses including one case mentioned above have undergone seroconversion after needlestick injuries[11–14]. All these occurred during the treatment of patients with AIDS or progressive generalized lymphadenopathy, all of whom were known to be HIV positive. These four cases all involved hollow needles, in some cases with syringe attached, and appear to have occurred during attempts to resheathe the needles. No instance of seroconversion after pricking with a surgical needle has been recorded, perhaps because a smaller volume of blood is introduced in such an injury.

We have no evidence that our attempts to reduce the risk of inoculation injury have prevented transmission of infection, but we feel it would be premature in our present state of knowledge to reduce these precautions in patients at risk of HIV or hepatitis B infection. The 29 per cent incidence of high-risk exposure to infection in our operating theatre staff would suggest, on the contrary, that we should make further efforts to reduce this exposure.

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Surgical anatomy of the human spleen

H. P. Redmond,
J. M. Redmond,
B. P. Rooney,
J. P. Duignan* and
D. J. Bouchier-Hayes*

*Departments of Anatomy and *Surgery, Royal College of Surgeons in Ireland, Dublin, Ireland*

Correspondence to:
Professor D. Bouchier-Hayes,
Department of Surgery,
Beaumont Hospital, Dublin 9,
Ireland

Post-splenectomy sequelae are now well recognized, and conservative splenic surgery is widely advocated. However, controversies exist regarding splenic surgical anatomy. We studied 127 human spleens using anatomical dissection and a sequential injection method involving both radiology and corrosion casting, with the primary aim of examining segmental splenic anatomy and blood supply. The existence of well-defined splenic segments was confirmed and these ranged in number from 3 to 7 with a mean of 4·3. Each segment had its own arterial supply and venous drainage. The segments were separated from each other by avascular planes. Subsegments with independent blood supply were also identified. The splenic artery was found to divide into two branches; in all cases these further divided into segmental arteries supplying the central segments of the spleen. The polar segments were supplied by segmental vessels of highly variable origin and size. This study aims to highlight the importance of identifying these segmental vessels at operation when splenic conservation is considered.

Keywords: Partial splenectomy, splenic blood supply, splenic segmentation

The phenomenon of post-splenectomy infection is now well recognized and many surgical techniques have been developed in an attempt to preserve splenic function. Recent studies suggest that partial splenectomy offers protection against pneumococcal sepsis[1–5]. While this is so, it remains a relatively rare operation, the main reason being that the spleen is a friable and highly vascular organ that can be difficult to mobilize, once haemorrhage has begun. Further advances in splenic conservation are dependent on better understanding of the vascular anatomy of the spleen.

The purpose of this study, therefore, was to identify accurately the segments of the spleen and their vascular supply.

Materials and methods

A total of 127 human spleens were studied, of which 50 were fresh post-mortem specimens; the remaining 77 were from dissection room cadavers. The spleens were isolated by division of the gastrosplenic and lienorenal ligaments and excision of the tail of the pancreas leaving splenic artery and splenic vein.

After removal, each spleen was studied using a number of techniques in a stepwise fashion. Firstly, macroscopic dissection was undertaken to identify the splenic vasculature and in particular the segmental vessels which were then cannulated to allow for the second and third stages of the procedure: radiological studies and corrosion casting. The following injections were performed (the number of investigations are given in parentheses): common splenic artery (8), common splenic vein (3), common splenic artery and vein (3), segmental arteries (26), segmental veins (3), segmental artery and vein simultaneously (10).

Radiological studies

Radiographs were taken with a mobile unit set at 3 kV for a 1·5 s exposure time at a distance of 0·914 m. The medium used was Conray Hypaque 420 (May and Baker Ltd., Dagenham, UK) which was injected into cannulae in a pattern as described above. Once the radiographs were completed, the cannulae were flushed with normal saline.

Corrosion casting

Using the same cannulae, injections were made using Batson's anatomical corrosion compound No. 17 (Polysciences Inc., Warrington, Pennsylvania, USA). Different colours were employed when individual segments were studied. Once injection was complete, the cannulae were clamped to prevent leaks and the spleens were submerged in water to allow the compound to take the natural form of the spleen. The cast material was then allowed to harden over 12–14 h. Each spleen was subsequently macerated in potassium hydroxide solution. The casts were then removed and any residual tissue washed away in warm water and detergent. Once the casts were dry they were photographed.

Results

Splenic vasculature

Common splenic artery: Figures 1 *and* 2. The splenic artery, henceforth referred to as the 'common splenic artery', arose as a single trunk from the coeliac axis in all but one case, where a second splenic artery was found arising directly from the aorta and supplying the upper pole. In the majority of specimens the artery was suprapancreatic, but in two cases it was retropancreatic and in one case it was intrapancreatic. The common splenic artery divided into a 'superior' and 'inferior' splenic artery in all cases.

Superior splenic artery: Figures 1 *and* 2, Table 1. The superior splenic artery was rarely a segmental artery and was usually

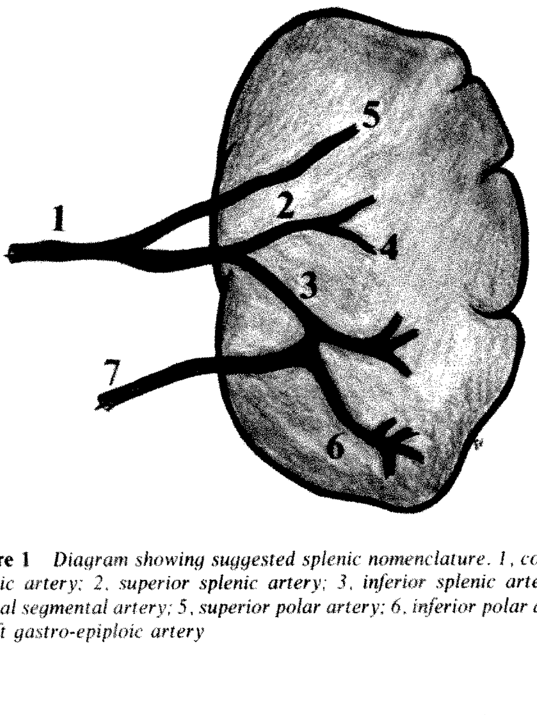

Figure 1 *Diagram showing suggested splenic nomenclature. 1, common splenic artery; 2, superior splenic artery; 3, inferior splenic artery; 4, central segmental artery; 5, superior polar artery; 6, inferior polar artery; 7, left gastro-epiploic artery*

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divided into segmental branches which then supplied the superior central segments of the spleen. In 60 per cent of specimens it gave off a branch to the superior pole of the spleen, which we termed the superior polar artery. It also gave off fundic branches to the stomach and, in one specimen, the left gastro-epiploic artery.

Inferior splenic artery: Figures 1 *and* 2, Table 1. The inferior splenic artery was smaller than the superior splenic artery. In the majority of specimens it divided into two segmental arteries supplying the inferior central segments. It gave origin to the inferior polar artery and the left gastro-epiploic artery in 28 and 3[illegible] per cent, respectively, of specimens studied.

Segmental arteries: Figure 1. Early studies showed the existence of well-defined segments within the spleen. The segmental vessels were either central or polar depending on the area of spleen they supplied.

1. *Central segmental arteries.* These vessels, like the polar arteries, took origin from the superior and inferior splenic arteries. Those arising from the former supplied the superior central segments, and those from the latter, the inferior central segments.
2. *Polar segmental arteries.* These vessels had a highly variable origin supplying the superior and inferior polar segments of the spleen.

Superior polar artery: Figure 2, Table 1. The superior polar artery supplied the superior polar segment. It was the more tortuous of the two polar vessels. Those having a proximal origin (36 per cent) arose from the superior splenic artery in 60 per cent of cases, the common splenic artery in 40 per cent of cases and in one instance from the aorta directly. Those originating distally (64 per cent) always arose from the adjacent superior central segmental artery, and were much smaller vessels than those arising proximally.

Inferior polar artery: Figure 3, Table 1. The inferior polar artery is always a segmental artery, having either a distal or a proximal origin. Those having a proximal origin (75 per cent) arose from either the common splenic artery (14·5 per cent), the inferior splenic artery (28 per cent) or the left gastro-epiploic artery (57·5 per cent). Those arising distally (25 per cent) always arose from the adjacent inferior central segmental artery.

Subsegmental vessels: Figure 1. Segmental arteries were found to divide into subsegmental vessels usually within the splenic capsule, but occasionally outside the splenic hilum, a pattern more common among the polar arteries and in those spleens containing many notches.

Patterns of splenic blood supply

There were three main patterns of blood supply. Firstly, and most commonly, the segmental arteries entered the hilum to supply their corresponding segments. In the remaining specimens the segmental vessels divided into subsegmental branches before entrance, or the superior and inferior splenic vessels entered the hilum directly before dividing into segmental vessels.

Common splenic vein. The pattern of vasculature for the splenic vein showed remarkable similarity to the artery. The veins ran a course identical to that of the segmental arteries, uniting to form the splenic vein which was retropancreatic.

Splenic segmentation: Figures 4–7. The existence of well-defined vascular segments in the spleen was suggested by radiological studies, further supported by corrosion casting and confirmed by microscopic examination of the intersegmental boundaries of the casts. These segments were defined as

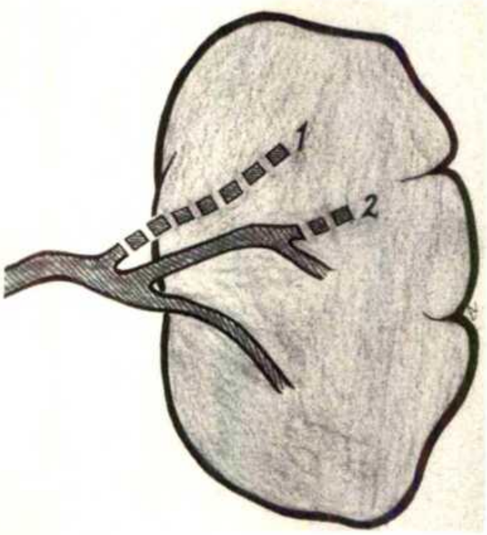

Figure 2 *Diagram showing origins of superior polar artery. 1, common splenic artery; 2, superior segmental artery*

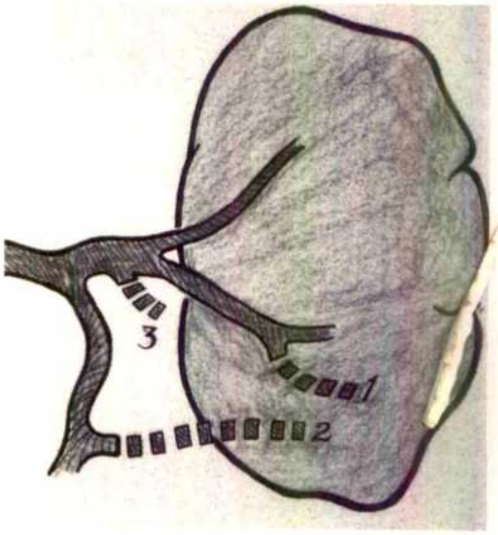

Figure 3 *Diagram showing origins of inferior polar artery. 1, inferior segmental artery; 2, left gastro-epiploic artery; 3, common splenic artery*

Table 1 *Origins of splenic vasculature*

Vessel origin	Superior splenic artery	Inferior splenic artery	Superior polar artery	Inferior polar artery	Left gastro-epiploic artery
Common splenic artery	100	100	39·8	14·5	35
Superior splenic artery	—	—	60·2	—	6·7
Inferior splenic artery	—	—	—	28	38·3
Superior polar artery	—	—	—	—	—
Inferior polar artery	—	—	—	—	20
Left gastro-epiploic artery	—	—	—	57·5	—

The values are percentages

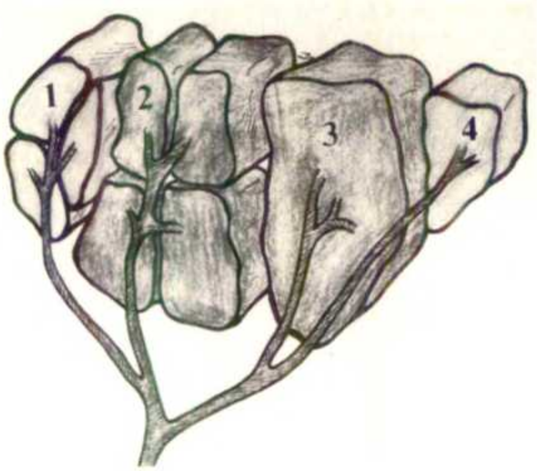

Figure 4 *Diagram illustrating segments and subsegments. 1, polar subsegment; 2, central subsegment; 3, central segment; 4, polar segment*

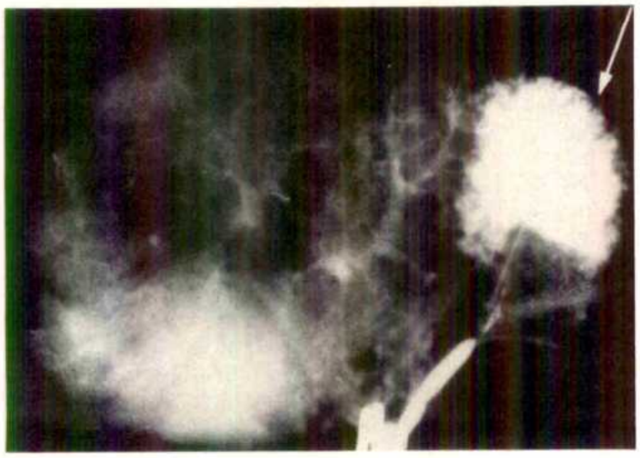

Figure 5 *Radiograph of polar segment. The arrow points to a polar segment*

anatomically distinct areas of splenic tissue running from the anterior to the posterior border, perpendicular to the long axis of the spleen. They ranged in number from three to seven (mean 4·3). There were two morphological types of segment—central and polar. The central segments were wedge-shaped in outline and larger than the polar segments. The number of these segments found in each spleen was variable (from one to five). Polar segments were pyramidal, located at the superior and inferior poles of the spleen, and were a constant finding.

On further study it was noted that each segment consisted of a number of 'subsegments'. There were three such units in polar segments and four in the central segments (*Figure 4*).

Spleniculi. When identified, spleniculi were also studied. They were present in 4 per cent of specimens and most commonly located in the gastrosplenic and lienorenal ligaments. Radiological and corrosion cast studies of these mesenchymal aggregates revealed them to have a striking similarity to subsegmental units in the spleen, both in blood supply and size.

Notches. Notches were found on the anterior and posterior borders, being more common along the former (range 1–7). The posterior border contained a maximum of two notches and frequently had none. Although the notches on the anterior border correlated well with segmental boundaries, this relationship was inconsistent.

Discussion

This study confirms the segmental nature of splenic anatomy, each segment being clearly separated from those adjoining it and having an independent arterial supply and venous drainage. It further demonstrates that these segments are composed of 'subsegmental units', each with an isolated blood supply.

The notched appearance of the spleen, not surprisingly, suggested splenic segmentation and this concept was evaluated as early as 1870 by Kyber[6] who described the spleen in man, cat, dog, horse and rabbit as being divided into several segments by 'fibrous septa'. Tait and Cashin[7] confirmed this in the dog and cat and in 1952 Dreyer and Budtz-Olsen[8] carried the concept a step further when they discovered separate venous segments while carrying out portal venography. Braithwaite and Adams[9], using radio-opaque dye injection, were the first to note that each splenic segment had its own arterial supply and venous drainage.

Recently, corrosion casting techniques have formed the basis for more detailed splenic segmental studies. While such studies confirm the existence of splenic segments they differ in their observations. Clausen[10], Gutierrez-Cubillos[11] and Gupta *et al.*[12] reported the existence of from two to four segments. Studies by Mikhail *et al.*[13] revealed up to five splenic 'lobes' while Voboril[14] found as many as ten splenic segments with a mean of six. Although splenic segmentation is now undisputed,

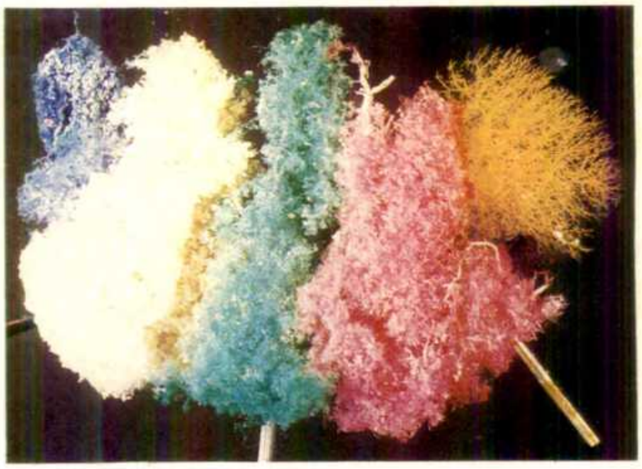

Figure 6 *Cast of a spleen containing five segments. Blue and yellow, polar; white, green and red, central. Note the avascular planes between segments*

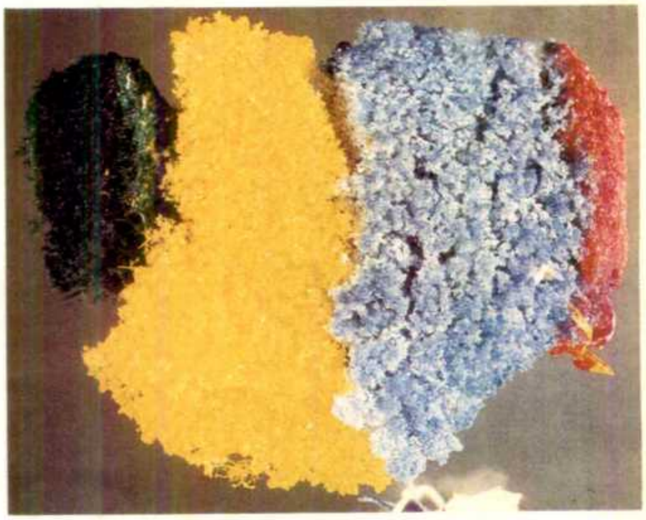

Figure 7 *Cast of a spleen containing four segments. Green and red, polar; yellow and blue, central*

there remains a lack of consistency in the literature regarding the exact morphology of these segments, their number and blood supply. We believe that lack of agreement on splenic segmental anatomy, as demonstrated above, is because of incomplete methodology and suggest that the segmental anatomy of the spleen can only be properly evaluated using a combination of techniques, as individual techniques have significant shortcomings.

With these points in mind, we studied the segmental anatomy of the spleen with the aid of macroscopic dissection, radiological studies and corrosion cast studies, using these techniques in a segmental stepwise fashion. As a result this study clearly identifies the existence of splenic segments; it defines them and classifies each one as either wedge-shaped (central) or pyramidal (polar). Synchronous injection studies of the segmental arteries and veins have further demonstrated the arterial and venous territories to have identical boundaries.

These further refinements of examination have led to the identification of 'subsegments', i.e. segments within segments with independent blood supply and venous drainage. The existence of these subsegments may have embryological relevance. When casts of subsegments were compared with those of accessory spleens or spleniculi, they were found to be similar both in appearance and in blood supply. This may imply that the embryological development of the spleen involves the amalgamation of these small units of splenic tissue (subsegments = spleniculi) to form segments and ultimately the entire organ. Any such units remaining, not incorporated into the organ, are isolated as accessory spleens or spleniculi.

Discrepancies also exist between previous studies regarding splenic blood supply[12,13]. The findings of this study indicate that the blood supply of the spleen has a predictable distribution depending on the number of segments present. This allows for clearer definition of splenic vascular anatomy than has hitherto been available. We suggest that the introduction of specific nomenclature as follows would facilitate the identification of splenic vasculature.

The 'common splenic artery' arises almost invariably from the coeliac axis in a common stem with the hepatic artery. It has two constant branches, the superior and inferior splenic, which subsequently divide into segmental arteries. Whereas central segmental blood supply is constant in origin, polar segmental supply is more variable, both in origin and vessel calibre. The other variable in splenic blood supply is the degree of incorporation of the division of the subsegmental and, to a lesser extent, the segmental vessels inside the hilum of the organ. This is responsible for the numerous patterns of vessel division found outside the splenic hilum, as referred to above.

We believe that the differences in opinion in the literature are a result of the misinterpretation of these very definite patterns of blood supply, coupled with the over-emphasis placed on recognition of segments from whole arterial or venous casts. This study demonstrates clearly the existence of definite patterns of splenic blood supply and offers a nomenclature in an attempt to clarify these. Finally, it implicates the segmental vessels as those with the greatest surgical importance and stresses that their early identification at operation for trauma should lead to increased splenic conservation.

Acknowledgements

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Intraperitoneal rupture of amoebic liver abscess

A. K. Sarda, S. Bal, A.K. Sharma and M. M. Kapur

Department of Surgery, All India Institute of Medical Sciences, New Delhi 110 029, India

Correspondence to:
Dr A. K. Sarda, 27 RPS, Triveni-I,
New Delhi 110 017, India

A retrospective analysis of 23 cases of amoebic liver abscess with intraperitoneal rupture is presented. Group I consisted of 16 patients with clinical features of generalized peritonitis. Eight of these patients were treated surgically, and four died. Group II consisted of seven patients with features of localized peritonitis and all were treated conservatively. In all cases the diagnosis of liver abscess was established by liver scan or ultrasound examination; peritonitis was established either at operation or, in the conservatively managed group, by aspiration of pus from the peritoneal cavity. Amoebiasis was diagnosed by serology. Eight group I and all group II patients were managed conservatively by aspiration of the liver abscess, antibiotics and amoebicides. There were no deaths in this group. It is suggested that, if the diagnosis can be made early, conservative treatment offers the best chance of cure for patients of amoebic liver abscess with intraperitoneal rupture.

Keywords: Liver abscess, amoebiasis, rupture, intraperitoneal

Liver abscess is the commonest extraintestinal manifestation of amoebiasis, a disease prevalent throughout tropical and subtropical countries. Peritonitis secondary to rupture constitutes the second most common complication of amoebic liver abscess after pleuropulmonary amoebiasis. Spontaneous rupture of amoebic liver abscess into the peritoneal cavity is reported in 2·5–17 per cent of patients[1], and the condition is frequently fatal with an associated mortality rate of up to 75 per cent[2]. Management of this complication of amoebic liver abscess has remained controversial. We present our experience with 23 cases of spontaneous rupture of amoebic liver abscess into the peritoneal cavity.

Patients and methods

Between 1981 and 1986, 240 cases of amoebic liver abscess were diagnosed and treated at our hospital. A retrospective analysis revealed that 23 of these cases had a spontaneous rupture of the abscess into the peritoneal cavity. The age and duration of symptoms at presentation, prodromal symptoms of fever and ill health with or without diarrhoea, and pain in the right upper abdomen were recorded. On the basis of signs at presentation the patients were divided into two groups: group I consisted of 16 patients with features of generalized peritonitis; group II consisted of seven patients with features of localized peritonitis.

Laboratory investigations included haemogram, liver function tests, stool examination and amoebic serology (haemagglutination test). The diagnosis of liver abscess was confirmed by Rose Bengal or technetium-99 hepatic scan. Diagnosis of peritonitis was based on the aspiration of pus from the peritoneal cavity in all cases. Since 1983 ultrasound examination has been used.

The indications for surgery included: (1) peritonitis when a liver abscess was not suspected; (2) failure to respond to conservative management; and (3) secondary infection. The surgical procedure consisted of drainage of pus from the peritoneal cavity and the liver abscess, a thorough peritoneal toilet with normal saline, and insertion of drains before closure of the abdomen. Other measures included administration of metronidazole and broad-spectrum antibiotics, followed by 21 days of chloroquine therapy. The remaining patients were managed conservatively with intravenous or oral metronidazole, antibiotics and needle aspiration of the liver abscess, with a follow-up treatment with chloroquine. All patients were followed up with hepatic scans and/or ultrasound examination to assess the response to treatment.

Results

The age of the patients ranged from 12 to 59 years; males were predominantly affected (male:female ratio, 19:4). The duration of symptoms at presentation ranged from 8 to 26 days. A history of ill health and fever (18 patients), diarrhoea (13 patients) and pain in the right lower chest and right upper abdomen (16 patients) were the most frequent symptoms. Amongst group I patients, five cases presented to the hospital with features of generalized peritonitis and two patients were referred from other centres in a moribund condition after failing to respond to conservative treatment; in one patient there was evidence of secondary infection in the aspirated pus. These eight patients underwent operation. In four of the remaining eight cases in the group, the diagnosis of a ruptured amoebic liver abscess was suspected because of tender hepatomegaly and ultrasound demonstration of a liver abscess. The other four patients developed features of peritonitis during the course of inpatient treatment of liver abscess. These eight cases were treated conservatively. The seven patients in group II were being treated at the hospital with a diagnosis of amoebic liver abscess and developed features of localized peritonitis confirmed by aspiration of pus from the peritoneum; these patients were also managed conservatively.

Laboratory investigations revealed leucocytosis ranging from 9500 to $26\,000/\text{mm}^3$ (mean $16\,000/\text{mm}^3$). The serum bilirubin was normal in 19 patients; in the remaining four cases serum bilirubin levels ranged from 3·2 to 5·6 mg/dl. The serum alkaline phosphatase (normal 3–13 KAU) was elevated in ten patients (range 17–347 KAU; mean 57 KAU) while the serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase was normal (40/40 units) in 17 cases and only minimally raised (maximum 90/95 units) in six cases. The serum albumin levels were below normal in 12 patients with a mean of 2·9 g/dl. The amoebic haemagglutination titre was determined in 22 patients and ranged from 1:1680 to 1:116 000 (considered positive if more than 1:512).

Hepatic scan (21 cases), ultrasound examination (11 cases) and computed tomography scan (one case) revealed that all patients harboured the abscess in the right lobe. In 21 cases the abscess was solitary while in two cases two abscesses were present. In all cases the abscess cavities occupied the superior portion of the right lobe.

All patients treated conservatively improved and follow-up hepatic scans revealed resolution of the abscess cavities within 3 months of discharge from the hospital. There was a high mortality rate in the surgically treated group with four patients succumbing to the disease. These included one patient with secondary infection who died from septicaemia, two patients who had failed to respond to conservative treatment and who died from their poor general condition, and another patient who developed multisystem organ failure with severe bleeding ten-

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dency postoperatively. The overall mortality rate from amoebic peritonitis was 17 per cent while it was 25 per cent in patients with generalized peritonitis. The duration of hospital stay was 11 ± 2 days for the surgically treated patients and 16 ± 3 days for those managed conservatively.

Discussion

Amoebic peritonitis following intraperitoneal rupture of a liver abscess is a serious complication. The reported incidence of this complication varies from 2·4 to 17 per cent[1,3–6]. In this series it was 9·6 per cent. This dreaded complication of amoebic liver abscess has been associated with a high mortality rate in the past, approaching 75 per cent[2,4,6]. The factors attributed to the high mortality are delayed or inadequate treatment[6,7], poor nutrition or diminished host resistance prevalent in most tropical countries associated with other diseases[6], and secondary infection with septicaemia[8]. The other poor prognostic signs are generalized peritonitis, jaundice, and the presence of multiple abscesses[4,9–11]. The causes of a 17 per cent mortality rate in the present series were delayed diagnosis, poor host resistance and septicaemia.

The diagnosis of the disorder may be difficult; in the present series the diagnosis was missed in 31 per cent of the patients presenting with generalized peritonitis. A high index of suspicion should always be maintained, especially in tropical countries. A useful pointer is the occurrence of the disorder almost exclusively in male patients[4] (83 per cent in the present series). A tender hepatomegaly, preceding history of diarrhoea, and a raised right dome of diaphragm may suggest an amoebic aetiology for the peritonitis[1] as was the case in the patients under review. A syndrome of abdominal pain of 'prerupture' has been described which may precede the development of peritonitis[12] although others point out that acute symptoms may be present without actual rupture[13]. Thus a correct diagnosis is often missed[1,11,12,14]. The pitfalls in the correct preoperative diagnosis as reported in literature have been analysed by Archampong[6] who observed that a preceding history of dysentery and of prolonged ill health may be absent whilst in endemic areas the common association of intercurrent disease may blur the picture, and that abdominal pain may not be confined to the right hypochrondrium before rupture.

Although the superior surface of the right lobe of the liver is the commonest site of involvement, abscesses that rupture into the peritoneal cavity usually involve the inferior surface of the liver[4]. Rupture is seen in a higher percentage of abscesses occurring in the left lobe of the liver[6,12,15–17]. The reasons cited are the smaller bulk of the left lobe which is unable to contain the rapidly expanding abscess, the complete peritoneal coverage of the left lobe and its anatomical relations which prevent the formation of firm adhesions, and a delay in the diagnosis of abscess located in this situation. However, in the present series all abscesses which ruptured were situated in the superior surface of the right lobe. Sudden rupture leads to generalized peritonitis while a slow leak allows formation of adhesions leading to localized peritonitis.

Conflicting opinions have been expressed concerning the treatment of amoebic liver abscesses which rupture into the peritoneal cavity. The indications for surgical intervention for amoebic liver abscess are, indisputably, left lobe abscesses and abscesses that are secondarily infected. However, there is no clear consensus regarding treatment of intraperitoneal rupture of amoebic liver abscesses. Since 1892, when Hulke first described successful operative treatment of such a case[14], many reports have appeared of surgical treatment of the disorder with good results[1,6,18–21]. However, since DeBakey and Ochsner's reports of 100 per cent mortality rate in patients treated surgically[4] many authors have stressed conservative measures[6]. The effectiveness of conservative treatment has been enhanced by the routine use of metronidazole which has been associated with the disappearance of the abscess cavity even without drainage, as demonstrated by repeated hepatic scans[22]. The present data would support these observations in that the mortality rate in surgically treated patients with generalized peritonitis was 50 per cent compared with a mortality rate of zero in patients managed conservatively. However, it is pertinent to emphasize that all the deaths occurred in patients in whom diagnosis was delayed and whose general condition was moribund. Thus, even though operative mortality has been reduced from 75–100 to 40–50 per cent[1] because of improved anaesthesia, resuscitative measures, antibiotics and antiamoebic drugs, data suggest that timely institution of conservative measures, particularly the use of metronidazole[2,6], offers the best chance of cure to patients with intraperitoneal rupture of amoebic liver abscesses, as was the case in the present series.

That amoebic liver abscess rupturing into the peritoneal cavity can kill is established, and this is corroborated by the death of 17 per cent of the patients under review. However, if a diagnosis is made early and antiamoebic treatment started, non-operative management can produce effective and gratifying results.

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Need for surgical wound dressing

H. Chrintz, H. Vibits,
T. O. Cordtz*,
J. S. Harreby†,
P. Waaddegaard and
S. O. Larsen‡

*Department of Surgery, Kalundborg General Hospital, Kalundborg, †Department of Surgery, Saeby General Hospital, Høng, and *National Centre for Hospital Hygiene and ‡Department of Biostatistics, Statens Seruminstitut, København, Denmark*

Correspondence to:
Dr H. Chrintz, Strandbakken 55,
DK-4400 Kalundborg, Denmark

The need for dressings on clean and clean contaminated surgical wounds was investigated. A total of 1202 patients with 1202 clean or clean contaminated surgical wounds were randomized into two groups: 633 wounds were covered by dressings up until the time of suture removal, and 569 wounds were treated without dressings after the first postoperative day. In the group characterized by long dressing time, the rate of postoperative wound infections was 4·9 per cent. The rate was 4·7 per cent in the group represented by short dressing time. Using short dressing time not only reduces the number of nursing hours but also limits the need for costly dressing material. In addition, both wound observation and patients' personal hygiene are made easier.

Keywords: Postoperative care, surgical equipment, wound healing, wound infection, surgical nursing

The covering of the primarily sutured surgical wound with a sterile dressing is ordinarily considered to be a routine conclusion to an aseptic operation. Most often, the wound is left dressed until the sutures are removed.

Purposes for wound dressings are: (a) absorption of wound secretions; (b) protection of the wound from injury; and (c) protection of the wound against bacterial contamination.

Experimental studies[1,2] have shown that the carefully sutured incision with haemostasis is sealed by fibrin within 6–24 h and that the wound hereafter becomes effectively protected against outside moisture and bacterial contamination.

It has not been proved that conventional dressings are capable of preventing the access of bacteria to the wound, nor that carefully sutured surgical wounds with haemostasis need this protection after 24 postoperative hours.

Previous clinical investigations have dealt with this issue partly by retrospective accounts of surgical wounds treated without dressings[3–5] and partly from comparative testings based on limited material[6–8]. Experimental tests have demonstrated a uniform healing between dressed and undressed surgical wounds[2].

At the present time, however, there are no published results of clinical investigations based on statistically sufficient material.

Patients and methods

The investigation was prospective and randomized. It was carried out on the surgical wards of Kalundborg General Hospital and Saeby General Hospital in the period from 1 November 1984 to 31 December 1987.

Before surgery, all patients were informed both verbally and in writing. Only those who gave their consent were entered. Patients under 3 years of age were exempt as were those with casts or any other type of immobilizing bandage.

The surgeon classified the wounds postoperatively as clean, clean contaminated, contaminated, or dirty, as indicated by Cruse[9]. Patients with clean or clean contaminated wounds were then randomly divided into two groups, according to their dates of birth: (a) even birth-date numbers: sterile dressings were applied to the wound from the end of the operation until the sutures were removed; (b) uneven birth-date numbers: sterile dressings were applied to the wound during the first 24 h, therafter being removed and the area left uncovered.

Drain sites were covered with sterile gauze until the drains were removed.

Patients' sex, age, height and weight were recorded. A patient was classified as being overweight if his weight in kilograms was greater than or equal to his height in centimetres minus 82. Height and weight were recorded in 1159 patients of whom 89 were overweight.

All patients were permitted to shower from the first postoperative day. Patients with dressings had them protected with a covering of plastic.

On suture removal, all cicatrices were examined for any signs of infection. A wound was defined as being infected by secretion of pus from the cicatrix, suture canals, or subcutaneous abscess.

Results

In all, 1325 patients were randomized. In 91, there was insufficient information at the time of removal of the sutures: 21 patients were incorrectly randomized; eight patients were withdrawn due to allergic reactions to the dressing material, and three patients died during the observation period. Thus 1202 patients remained for the final analysis.

Tables 1 and *2* show the distribution of patient characteristics, the total incidence of wound infections, and the operations performed. Overweight patients had a significantly increased infection rate, with nine of 89 obese patients developing wound infections (χ^2 test, $P=0{\cdot}021$). Sex, age or the degree of contamination had no significant influence on the infection rate.

Table 3 shows the incidence of wound infection in patients with long and short dressing times. There is no significant difference between the infection rate in the two groups. In 1·8 per cent of the wounds there was an accumulation of pus that required surgical drainage. In the remainder of the infected wounds the infection did not influence treatment.

Table 4 shows the number of patients in the two treatment groups who received a dressing change on the ward, together with the reasons for that dressing change; 108 patients performed their own dressing change after discharge from hospital.

No patient without a dressing needed to have one applied as a result of secretion from the wound or injury to it.

Table 1 *Distribution of patients in the randomized groups*

	Total	Wound dressed	Wound exposed	Infected wounds
No. of patients	1202	633 (52·7)	569 (47·3)	58 (4·8)
Clean wounds	876	465 (53·1)	411 (46·9)	42 (4·8)
Clean contaminated wounds	326	168 (51·5)	158 (48·5)	16 (4·9)
Women	629	331 (52·6)	298 (47·4)	26 (4·1)
Men	573	302 (52·7)	271 (47·3)	32 (5·6)
Age <50 years	721	360 (49·9)	361 (50·1)	31 (4·3)
Age ⩾50 years	481	273 (56·8)	208 (43·2)	27 (5·6)
Not overweight	1070	556 (52·0)	514 (48·0)	49 (4·6)
Overweight	89	54 (61)	35 (39)	9 (10)

Figures in parentheses are percentages

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Table 2 *Surgical procedures performed*

Type of operation	Wound dressed (633 wounds)	Wound exposed (569 wounds)	Total
Herniotomy	221	202	423
Appendicectomy	83	74	157
Caesarian section	43	45	88
Resection of fallopian tubes, ovaries or salpingo-oophorectomy	34	52	86
Resection of the breast or mastectomy	37	29	66
Hysterectomy	25	32	57
Cholecystectomy	29	19	48
Extracio venae saphenae magnae	26	22	48
Osteosynthesis colli femoris	30	16	46
Others (44 different surgical procedures)	105	78	183

Table 3 *Wound infections*

	Wound dressed (633 wounds)	Wound exposed (569 wounds)	Total
Infected wounds	31 (4·9)	27 (4·7)	58 (4·8)
Surgical intervention needed	12 (1·9)	10 (1·8)	22 (1·8)

Figures in parentheses are percentages

Table 4 *Change of dressings on the surgical wards*

Reasons	Wound dressed (633 wounds)	Wound exposed* (569 wounds)
Dressing wet	148 (23·4)	16 (2·8)
Inspection of wound	44 (7·0)	— —
Others	14 (2·2)	— —
Total	206 (32·5)	16 (2·8)

Figures in parentheses are percentages. * Dressing during the first 24 postoperative hours

Discussion

The results of this investigation show that clean and clean contaminated primarily sutured wounds treated by the application of a dressing during the first 24 h after operation and thereafter left undressed do not have an increased incidence of wound infection in relation to the same type of wounds which are dressed until suture removal. Previous studies have shown the same result, but either the investigations have not been controlled[3–5] or the material has been too limited and the patients not randomized[6–8].

Some authors stress the risk of cross-infection on the ward[10–13]. If a conventional wound dressing protects sutured surgical wounds against this risk after 24 postoperative hours then the infection rate would have been higher in those patients who were treated without dressing. We can therefore conclude that either the dressing adds no protection against cross-infection, or the risk of cross-infection is low and non-existent during the investigation period.

Routine treatment of sutured surgical wounds with dressings is based on tradition and is not scientifically supported. The advantages of omitting a dressing after the first 24 postoperative hours are: (a) the wounds can be easily examined with no unnecessary inconvenience to the patient, and the earliest signs of wound complications can be noted; (b) the method not only reduces the number of nursing hours used to change dressings but also limits the need for dressing material; and (c) patients without dressings are more easily able to carry out their personal hygiene. The presence of a 24-h-old sutured wound is not a contraindication to washing or showering[3,8,14].

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Paper accepted 10 October 1988

Correspondence

Enterostomy as an adjunct to treatment of intra-abdominal sepsis

Sir

We were interested to read the paper by Hesp *et al.* (*Br J Surg* 1988; **75**: 693–6). However, we were surprised to read that no data concerning the results of this technique were available in the literature.

In the Surgical Digestive Intensive Care Unit of the Hôpital Saint-Antoine, Paris, France, temporary enterostomies have been used since 1969 for this indication[1]. Many papers describing the results of this approach, together with the technique of chyme reinfusion, have been published in both French and English literature[2,3]. It is disappointing to see that the information on this subject does not appear to have been exhaustively researched before publication.

P. Frileux

Hôpital Saint-Antoine
Paris Cédex 12
France

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Anatomical nit-picking?

Sir

In a survey of 30 anatomical or surgical textbooks regarding the surface anatomical marking of the deep inguinal ring, 14 stated that it was at the mid-inguinal point and nine that it was at the mid-point of the inguinal ligament. Six books gave no surface marking for the deep ring and one modestly or perhaps correctly stated that it was difficult to be sure.

The other structure positioned at either of those two landmarks is the femoral artery and, again, with this the picture is almost as confused, with 18 putting it at the mid-inguinal point and only five at the mid-point of the inguinal ligament.

The difference between the mid-inguinal point and the mid-point of the inguinal ligament is often practically non-existent (even a modest covering of adipose tissue can make the bony points difficult to locate without causing undue discomfort to the patient) and, therefore, it seems a rather archaic and even futile exercise to retain the two as separate entities. To be pedantic, the mid-inguinal point should actually be just above the inguinal ligament and thus pulsation felt at that point would be that of the external iliac artery and not the femoral artery.

Surely it would be sensible to favour a more pragmatic approach, and teach students that when feeling for femoral artery pulsation and when attempting to occlude the deep ring in examination of hernias, they should use two fingers and therefore actually cover both anatomical points?

P. D. Scott

Manchester Royal Infirmary
Manchester M13 9WL
UK

Growth rates in hepatic metastases

Sir

We would like to make some comments on the paper by Finlay *et al.* (*Br J Surg* 1988; **75**: 641–4) on growth rates in hepatic metastases.

First, the formula for volume appears to be incorrect. There should be three length dimensions in any volume formula; for example, a spherical metastasis with diameter a would have volume $V=\frac{\pi}{6}a^3$, an oblate or prolate ellipsoid with diameters a and b would have volume $V=\frac{\pi}{6}ab^2$ and a triaxial ellipsoid with diameters a, b and c would have volume $V=\frac{\pi}{6}abc$. Should the formula given be volume $V=\frac{\pi}{6}ab((a+b)/2)$?

Second, although it is stated that at least three serial volume measurements were made for each patient and metastasis, only two points are shown for most of the growth curves in *Figures 1* and *2* and *Tables 1* and *2*. The instantaneous doubling time calculated depends on whether the exponential parameter was estimated from all serial data points or from just two, in which case, which two? The way dt differs from the first two data points to the last two may give some support to using the Gompertz equation as it would imply that dt is changing with volume.

Third, there are some important discrepancies between the data given and the statistical conclusions. Correlation coefficients are normally expressed in a range from -1 to $+1$ so it is not clear what a value of 90·54 means: is it a percentage? Indeed, were it not for a missing extreme value on the scatter plot (*Figure 3*), the correlation would not be significant, as is the case for overt and occult taken separately. While the overall values for growth rates seem plausible, the distinction between overt and occult seems entirely artificial and the difference in Dt between them is not significant ($P<0{\cdot}07$ Mann–Whitney U test).

Finally, as stated, back extrapolation is such a precarious exercise that one wonders about the usefulness of the information which is gained in this way.

C. J. Pritchett
S. Y. Coleman

Queen Mary Hospital
Hong Kong

Surgical glove perforation

Sir

I read with interest the paper by R. D. A. Dodds *et al.* concerning surgical glove perforation (*Br J Surg* 1988; **75**: 966–8). It is disturbing that in 50 per cent of cases they found that the surgeon was unaware that a perforation had occurred. This figure is comparable with the experience of other authors[1,2]. Gloves may even be perforated before being donned.

In the light of the ever increasing number of HIV- and hepatitis B-positive patients, it would be most desirable to be made aware of a glove puncture as soon as it occurred so that gloves could be changed immediately, thus preventing prolonged contact of the patient's body fluid with the surgeon's skin. Likewise, cotton gowns and drapes are not impervious to organisms, particularly when they are wet[3].

An electronic device intended to detect direct contact of the patient's body fluids with the surgeon's skin has been described, where a breakdown in the normal very considerable electrical resistance between surgeon and patient, as a result of direct fluid contact between the two, causes an audible alarm to sound[4]. I am able to report preliminary experience of its use in 51 cases.

The alarm sounded 41 times in 17 cases, the maximum number per case being five. Glove punctures (determined by inflation under water) were responsible on 11 occasions (five when double-gloved, i.e. punctures through both pairs), and damp gown sleeves touching the wound caused 29 alarms. The device sounded only once without explanation.

The device, which is simple to use, could have application when operating on 'high-risk' patients, as well as in prosthetic surgery where small inoculi of normal commensal organisms may cause serious postoperative sepsis.

It has been suggested that the wearing of double gloves confers additional protection to the surgeon against contact with the patient's body fluids[5]. Double gloving is not, however, universally acceptable, with possible discomfort and reduced sensitivity and dexterity leading to the surgeon removing his gloves in 26 per cent of cases[5].

The use of this device would allow the surgeon to wear a single pair of gloves if he so desired, being warned as soon as a perforation came into contact with the patient's body fluid, even if he did not feel anything when the puncture occurred. The device has also been shown to be capable of detecting punctures through two pairs of gloves, and in addition warns of wet gown sleeves touching the wound, of which the surgeon may be unaware. The latter was detected on almost three times as many occasions as gloves puncturing. Fluid leakage through gowns has largely been ignored in recent publications concerning surgeons' safety[5,6].

A. J. Hamer

University of Bristol Medical School
Bristol BS8 1TD
UK

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Branchial cysts in the parotid gland

Sir

We enjoyed the paper by Wyman and his colleagues (*Br J Surg* 1988; **75**: 818–19) which draws attention to branchial cysts within the parotid gland. It is a pity that they give no indication of the incidence of the condition as we believe it to be rather higher than previously reported. We found five cases out of 133 consecutive parotidectomies, an incidence of 3·8 per cent[1]. It is implied that preoperative diagnosis cannot easily be made but, with clinical awareness of the condition supported by ultrasound scanning and needle cytology, the condition can be diagnosed before surgery.

We agree that the lymph node or inclusion hypothesis is the most likely explanation for branchial cysts within the parotid. While of interest, this has little influence on diagnosis or treatment. Most of these cysts will probably continue to be found by chance in superficial parotidectomy specimens, but awareness of their existence may allow more to be treated by simple cystectomy alone.

Since our report we have detected another case preoperatively.

M. Thomas

St. Peters Hospital
Chertsey
Surrey KT16 0PZ
UK

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Graft–enteric fistula

Sir

We read with great interest the paper by Tilanus *et al.* on the diagnosis and management of graft–enteric fistula (*Br J Surg* 1988; **75**: 915–6). The authors confirmed the appalling mortality from this condition and report one survivor of ten patients who underwent graft excision and subsequent extra-anatomic bypass for graft–enteric fistula of the proximal anastomotic line. Greater success was reported with local treatment for the distal anastomotic line (five out of six survivors).

We agree that every patient who presents with blood loss in the gastrointestinal tract after vascular prosthetic implantation needs a thorough work-up and laparotomy to exclude the diagnosis of graft–enteric fistula. We support the authors' view that gastroduodenoscopy is the most important preoperative diagnostic test which may not only exclude other more common causes of gastrointestinal haemorrhage, but may also actually visualize the graft in the fourth part of the duodenum. Arteriography is rarely helpful in the diagnosis of this condition when the patient is stable. We have found that CT scanning is of considerable help and in our experience the fistula may be imaged by this technique.

Surgical intervention for aortoenteric fistula is mandatory since eventual exsanguination is inevitable. Most series suggest that there is usually a significant time period between diagnosis and operation when the patient is stable. This gives the surgeon an opportunity to plan the best management of such cases. The removal of all prosthetic material combined with adequate postoperative drainage remains the procedure of choice. Protection of the distal circulation by extra-anatomic bypass (usually axillobifemoral bypass) is recommended. In contrast to Tilanus *et al.* we believe that extra-anatomic bypass should be inserted under aseptic conditions before exploratory laparotomy and graft excision. By this method the mortality rate may be reduced to around 17 per cent[1]. Two such cases have recently been managed by this method with success.

To prevent aortic stump blow-out we meticulously oversew the aortic stump with interrupted monofilament sutures followed by a continuous layer and finally a seromuscular patch using the anterior longitudinal spinal ligament. Adequate postoperative drainage and suitable antibiotic cover are mandatory.

Prevention of this aortoenteric fistula remains the primary goal. In particular it is vital to protect the suture line either by wrapping the aneurysmal sac around the prosthesis, or by interposing omentum between the bowel and graft. Strict asepsis during aortic procedures is mandatory and if the bowel is transgressed for any reason then the operation is best abandoned. Once the diagnosis of aortoenteric fistula is diagnosed or suspected, early aggressive surgery remains the only hope for decreasing the mortality rate in the long term.

P. M. Dawson
R. M. Greenhalgh

Charing Cross and Westminster Medical School
London W6 8RF
UK

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Pulsatile varicose veins associated with tricuspid regurgitation

Sir

R. L. Blackett and G. E. Heard (*Br J Surg* 1988; **75**: 865) presented two interesting cases of pulsatile varicose veins associated with tricuspid regurgitation. They suggested that it should be possible to exclude an arteriovenous fistula from tricuspid regurgitation in the absence of a characteristic machinery murmur.

We report a similar case where a 69-year-old man, with previous rheumatic fever, developed aortic and mitral valve disease, culminating in Starr–Edwards valve replacement in 1974. He presented to the casualty department with brisk bleeding from left-sided varicose veins which were noted to be grossly pulsatile with an audible continuous bruit overlying the saphenofemoral junction. He had apparently had varicose veins for many years and had been largely asymptomatic apart from some eczema and an early ulcer on his left calf. He was noted to have had cardiac catheterization in 1987 and a presumptive diagnosis of arteriovenous fistula was made. His bleeding having been controlled he was admitted to our unit the following week and it was at this point that an 8 cm jugular venous pressure diastolic murmur at the left sternal edge, pulsatile hepatomegaly to 4 cm and bilateral ankle oedema were noted. He also had less marked right-sided varicose veins which were also pulsatile and had a notable overlying bruit. Although it was probable that tricuspid regurgitation was responsible for this patient's pulsatile varicose veins, it was decided that he would benefit from surgical treatment. He proceeded to exploration of his left groin which revealed no evidence of any arteriovenous fistula, and high saphenous ligation, stripping and multiple excisions were performed.

The points raised by this case are first that it was the presence of a murmur overlying his varicose veins which initially delayed the correct diagnosis. It would appear that although the absence of a murmur may allow the exclusion of an arteriovenous fistula its presence does not allow the exclusion of a cardiac cause. Second, patients with marked venous back pressure are going to develop severe varicose veins with their associated problems if they have high saphenous incompetence and are probably better having these veins treated.

At the time of review this man's leg swelling had considerably reduced, his ulcer had healed and he had symptomatically benefited from having had the procedure performed.

G. W. Hollins
J. Engeset

Aberdeen Royal Infirmary
Aberdeen AB9 2ZB
UK

Single duct discharge from the nipple

Sir

In reply to the letter by Chaudray and Fentiman (*Br J Surg* 1988; **75**: 1044) we are interested to read that they consider a haemoglobin-positive discharge requires further investigation by microdochectomy. All the letter lacks is the backing of this fact. We have given the results of an audit of microdochectomy in 170 cases and given our recommendations for management based on this. We would like to see a similar audit by Messrs Chaudray and Fentiman to substantiate their claim, regarding the value of testing for haemoglobin in nipple discharge.

A. P. Locker
R. W. Blamey

Nottingham Health Authority City Hospital
Nottingham NG5 1PB
UK

Book reviews

Textbook of Uncommon Cancer

C. J. Williams. 176 × 255 mm. Pp. 1028. Illustrated. 1988. Chichester: John Wiley. £110.00.

The aim of this 1000-page textbook is to 'collect together comprehensive and critical reviews on many of the rare tumours'. It is primarily aimed at the busy clinician, who needs an immediate reference source of more than one or two paragraphs, and a way into the literature.

Dipping into the book to read about my favourite tumours, it seems on the whole remarkably successful. There is a strong clinical bias to most of the chapters, but the opinions are balanced and the references up to date. Rare tumours often provide an opportunity to understand something about biology. Confusing topics like the primitive neuroectodermal tumours are presented clearly and in a way which I think would be helpful to the researcher in neurobiology as well as to the clinician. Many chapters (although not all) include excellent short reviews of aetiology and pathobiology, and even genetics.

The book is well produced: the binding is sturdy, the index works, and the photographs and diagrams are adequately reproduced. I would recommend this as a book for hospital libraries, for the oncology unit, and for the shelves of laboratories where scientists are confused about the difference between a ganglioneuroma and a neuroblastoma.

At £110 this is hardly a book for an individual to purchase, but for a library I think it is good value.

B. A. J. Ponder

The Institute of Cancer Research: Royal Cancer Hospital
Sutton SM2 5PX
UK

Perspectives in Shock Research

R. F. Bond, H. R. Adams, I. H. Chaudry. 158 × 232 mm. Pp. 431. Illustrated. 1988. New York: A. R. Liss. $90.00.

Attracted by the title, a surgeon might well pick up this book, particularly when he found that it was the report of the proceedings of the Tenth Annual Conference of the American Shock Society and the First International Shock Congress, 1987, sponsored by the Shock Societies of America, Europe and Japan. However, although the contents of this book are much more clinical than those of its nine predecessors, they might surprise the typical surgeon.

He should be interested in the four papers dealing with the Veterans' Administration Cooperative Study No. 209 and the difficulty of trying to decide whether corticosteroids are of therapeutic value in serious sepsis. The overall answer seems to be that they are not but a number of subsidiary questions remain. There is a section of detailed biochemistry on the cellular aspects of shock and on the involvement of the central nervous system, but what of all the papers dealing with the possible roles of eicosanoids, endogenous opioids, complement, activated macrophages and the interleukin family and the whole question of 'mediators'? These are areas of research where the general surgeon seems to play no part and is conspicuous by his absence not only from meetings of this type in North America but from those in Europe as well. The geographical distribution of the abstracts accepted for this Congress in Montreal is of interest: America (North and South), 159; Europe (excepting UK), 34; Japan, 21; China, 6; Middle East, 6; UK, 5. Is the British surgeon right to hold aloof from this field of research? (Some American surgeons would agree with him but their number seems to be falling.) This question is perhaps a reason for reading this book.

H. B. Stoner

Emeritus Professor
Hope Hospital
Manchester
UK

Bailey and Love's Short Practice of Surgery. 20th ed.

A. J. Harding Rains and C. V. Mann. 168 × 248 mm. Pp. 1406 + xii. Illustrated. 1988. London: H. K. Lewis. £35.00.

This was the textbook recommended by my surgical teachers both for M. B. surgery and for the final fellowship examination. This is perhaps indicative of my age because I rarely suggest that our present undergraduates purchase such a large and comprehensive book. Most students now rely instead on lecture notes or the excellent *Principles and Practice*.

What of the fellowship candidate? I recently took a straw-poll on the St. Thomas' fellowship course and it was apparent that 'Bailey and Love' is still extremely popular despite the fact that a number of new rivals have recently appeared on the scene.

What then is the secret of this book's phenomenal success? I think this is related to a number of factors, not least of which is its price. If the cost of other large textbooks is taken as a fair guide, then either 'Bailey and Love' is literally being given away, or the publishers of the other books are making an excessive and unjustifiable profit. To some extent the prowess of the book is obviously responsible, because a large print run and guaranteed sales allow a lower profit margin, but this does not seem to be the whole story. Whatever the reason, H. K. Lewis and Company is to be commended on the amazing value of its flagship publication.

Anyway, enough of dull fiscal matters, what of the book? Well, it is still easily recognizable as the infant of its distinguished forebears. There can be little complaint that it retains its title, for when I compared the present 20th edition with my 12th edition, large portions of the text remained unaltered. This is commendable where there has been little in the way of advance, but a textbook rapidly dies when it fails to keep pace with recent developments. There is little to fear on this score in this book; the two main editors have now assembled a large selection of sub-editors or section editors who have ensured that the text is up to date in providing an overview of surgical diagnosis and management in 1988. For example, both extracorporeal shock-wave lithotripsy and balloon angioplasty receive adequate coverage, though I would quibble at the scant attention paid to distal arterial bypass surgery and the place of liver resection in liver neoplasia.

In general the book is slightly uneven, and this reviewer's bias is perhaps revealed if he finds the chapters on arterial disease, venous disease and lymphatic disease the least satisfactory. The orthopaedic section has always been weak, and I found little evidence that this has been rectified in the new edition. I will continue to recommend that fellowship candidates purchase a separate orthopaedic text. In sharp contrast it seemed to me that the chapters devoted to urology were particularly strong.

I have never really liked the presentation or layout of the book and this too remains unchanged, with large tracts of 'small print' and myriads of tiny figures often of indifferent quality. I also must confess to an aversion to the footnotes recording the names of the 'famous' without reference to their published work—as an aside it is interesting to see whose names remain and whose disappear in succeeding editions. How are the mighty fallen!

Despite these criticisms, with which not all will agree, the book will, I am sure, remain a best seller. The tried and trusted formula has always worked until now, though I cannot help feeling that it is time for some radical surgery if the long-term future of this book is to be guaranteed, and it is to continue to outsell all its rivals.

K. G. Burnand

Assistant Director
Surgical Unit
St. Thomas' Hospital
London SE1 7EH
UK

Colour Atlas of Gastrointestinal Pathology

B. C. Morson. 220 × 280 mm. Pp. 290. Illustrated. 1988. Oxford: Oxford University Press. £75.00.

This is a volume in a series known as 'The Oxford Colour Atlases of Pathology'. The series is aimed at the clinical pathologist and postgraduates specializing in pathology.

The book is beautifully produced with almost 600 colour illustrations of both excised surgical specimens and histopathological appearances. The photographs are clear and remarkably well reproduced. Each illustration has a well written explanatory legend. As is appropriate in an atlas, about 80 per cent of the contents is occupied by the illustrations and their legends. Interposed between each group of illustrations are short areas of text which introduce each topic. The book confines itself to the diseases from the oesophagus to the anus but does not include diseases of the associated organs such as liver or pancreas.

Anyone interested in gastrointestinal pathology will enjoy dipping into this book. I believe it will be a useful reference work in many pathology departments.

P. Schofield

Consultant Surgeon
Withington Hospital
Manchester
UK

Notices and announcements

24 February 1989
Femoro-popliteal Bypass: Can Better Assessment Lead to Improved Results?
Leicester, UK
Information: Miss Rosalind Aldwinckle, Secretary to Professor P. R. Bell, University of Leicester School of Medicine, Department of Surgery, Clinical Sciences Building, The Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, UK

25–26 February 1989
Second Annual Congress on the North American Society of Phlebology
New Orleans, USA
Information: Pat Curl, Course Coordinator, North American Society of Phlebology, 3960 Park Boulevard, Suite E, San Diego, California 92103, USA

4–11 March 1989
7th Winter Congress: Diagnostic Imaging
Courchevelle, France
Information: Ms Mary Ullman, Winter Congress, 21915 Roscoe Boulevard, Suite 222, Canoga Park, California 91304, USA

5–7 March 1989
Surgical Masterclass for Consultants and Senior Registrars in General Surgery
Aviemore, U.K.
Information: Clerk to the College, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

5–10 March 1989
Magnetic Resonance Imaging Update 1989: Winter Conference
Snowbird, Utah, USA
Information: Radiology Postgraduate Education, Room C324, University of California, San Francisco, California 94143-0628, USA

11–18 March 1989
7th Cardiosurgical Symposium in Zurs
Zurs, Austria
Information: Professor Dr M. Deutsch, Abtlg fur Herz-Gefass und Thoraxchirurgie, Krankenhaus der Barmherzigen, Schwestern vom Heiligen Kreuz, Grieskirchner Strasse 42, A 4600 Wels, Austria

12–15 March 1989
Current Problems in Breast Cancer
Vienna, Austria
Information: Secretariat ICS, Elisabeth Ribar-Maurer, c/o Wiener Medizinische Akademie, Alser Strasse 4, A 1090 Vienna, Austria

27–31 March 1989
Neuroradiology at Vail
Vail, Colorado, USA
Information: Janice Ford or Nancy Fedullo, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA

29–31 March 1989
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information: The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

6–9 April 1989
4th ASEAN Otorhinolaryngological Head and Neck Congress
Singapore
Information: Dr R. E. Stanley, Organizing Secretary, c/o ENT Department, Singapore General Hospital, Singapore 0316

22–28 April 1989
Critical Care in the 1990s
Aruba, Dutch Caribbean
Information: Dr Omar Prakash, Thorax Centre, Erasmus University, PO Box 1738, DR Rotterdam, The Netherlands

24–27 May 1989
8th Annual Meeting of the American Association for Cancer Research
San Francisco, California, USA
Information: American Association for Cancer Research, 530 Walnut Street, 10th Floor, Philadelphia, Pennsylvania 19106, USA

4–17 June 1989
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information: Dr J. F. Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 13214, USA

12–13 June 1989
Cholelithorama: Total Gallstone Management
London, UK
Information: BDI Conferences Ltd., 3 Beaconsfield Terrace Road, London W14 0PP, UK

19–21 June 1989
Tripartite Meeting
Birmingham, UK
Information: Mr Roger Grace, The Royal Hospital, Wolverhampton, UK

21–23 June 1989
71st Annual Meeting of The Endocrine Society
Seattle, Washington, USA
Information: The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

24–27 June 1989, 28–30 June 1989
Second Mediterranean Surgical Congress
Athens, and continued in Heraklion, Crete, Greece
Information: Ms Peggy Alexopoulou, Public Relations Centre, 56 Hippocratous Street, 106 80 Athens, Greece

2–15 July 1989
Neonatal and Paediatric Surgery
Manchester, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

15–16 July 1989
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27 August–1 September 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Information: International Congress and Convention Association, PO Box 50006, Tel Aviv 61500, Israel

6–8 September 1989
Fourth World Congress of the International Society for Diseases of the Oesophagus
Chicago, Illinois, USA
Information: 4th World Congress of the International Society of Diseases of the Oesophagus, 911 Busse Highway, Park Ridge, Illinois 60068, USA

10–15 September 1989
3rd International Symposium on Inflammatory Bowel Diseases
Jerusalem, Israel
Information: International Congress and Convention Association, P.O. Box 50006, Tel Aviv 61500, Israel

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Belfast, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

21–23 September 1989
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Cardiff, Wales, UK
Information: Mr Taylor, Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr Joseph W. C. Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

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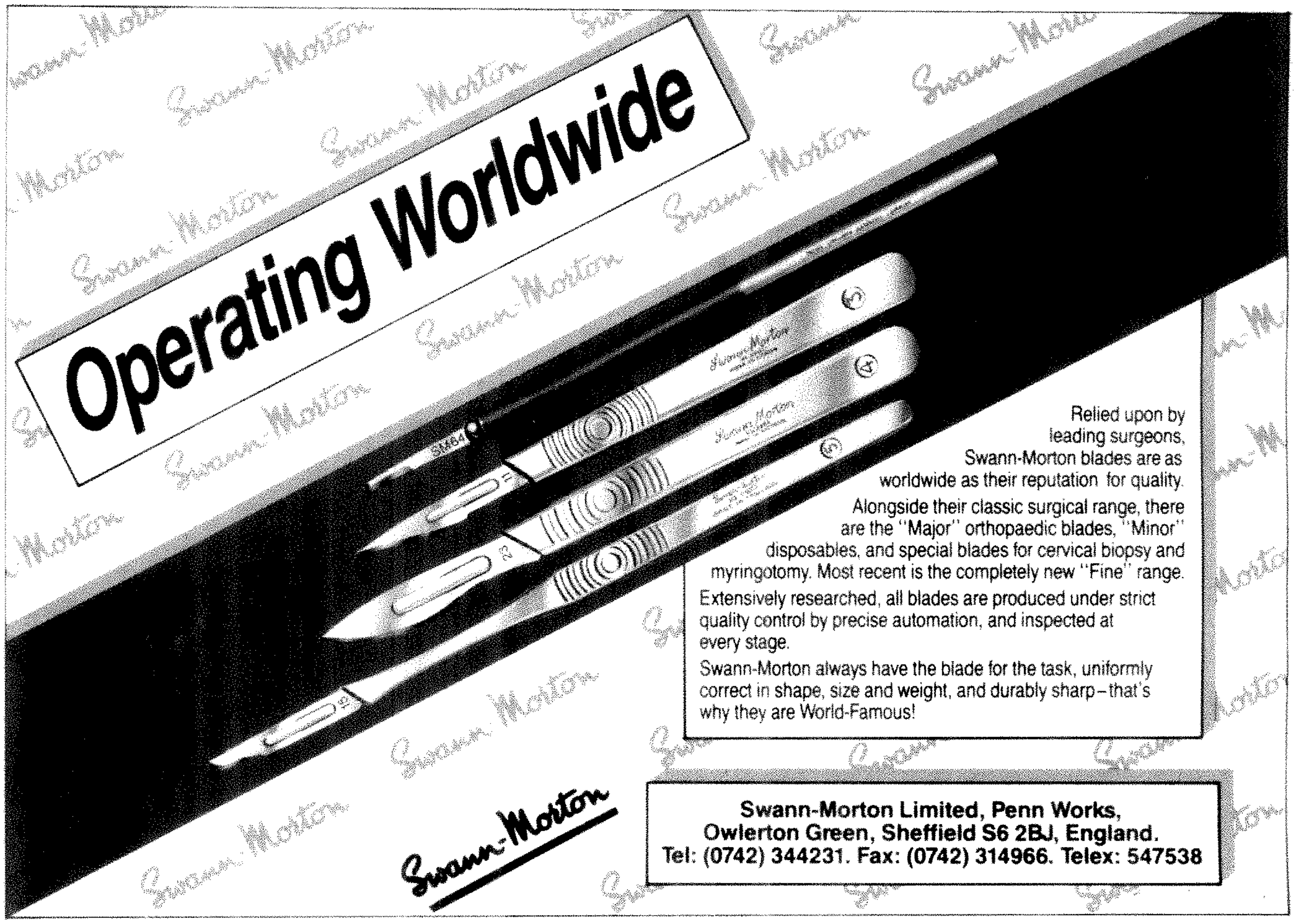

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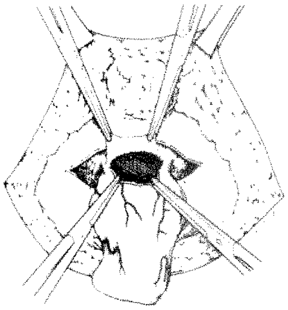

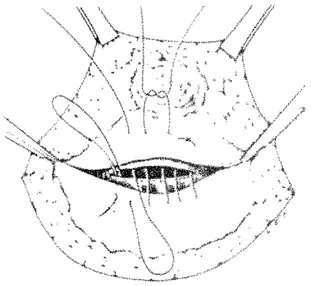

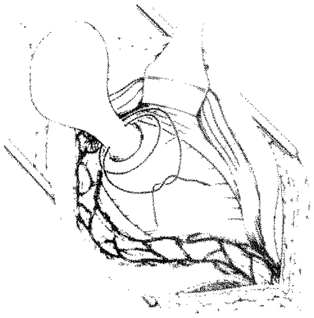

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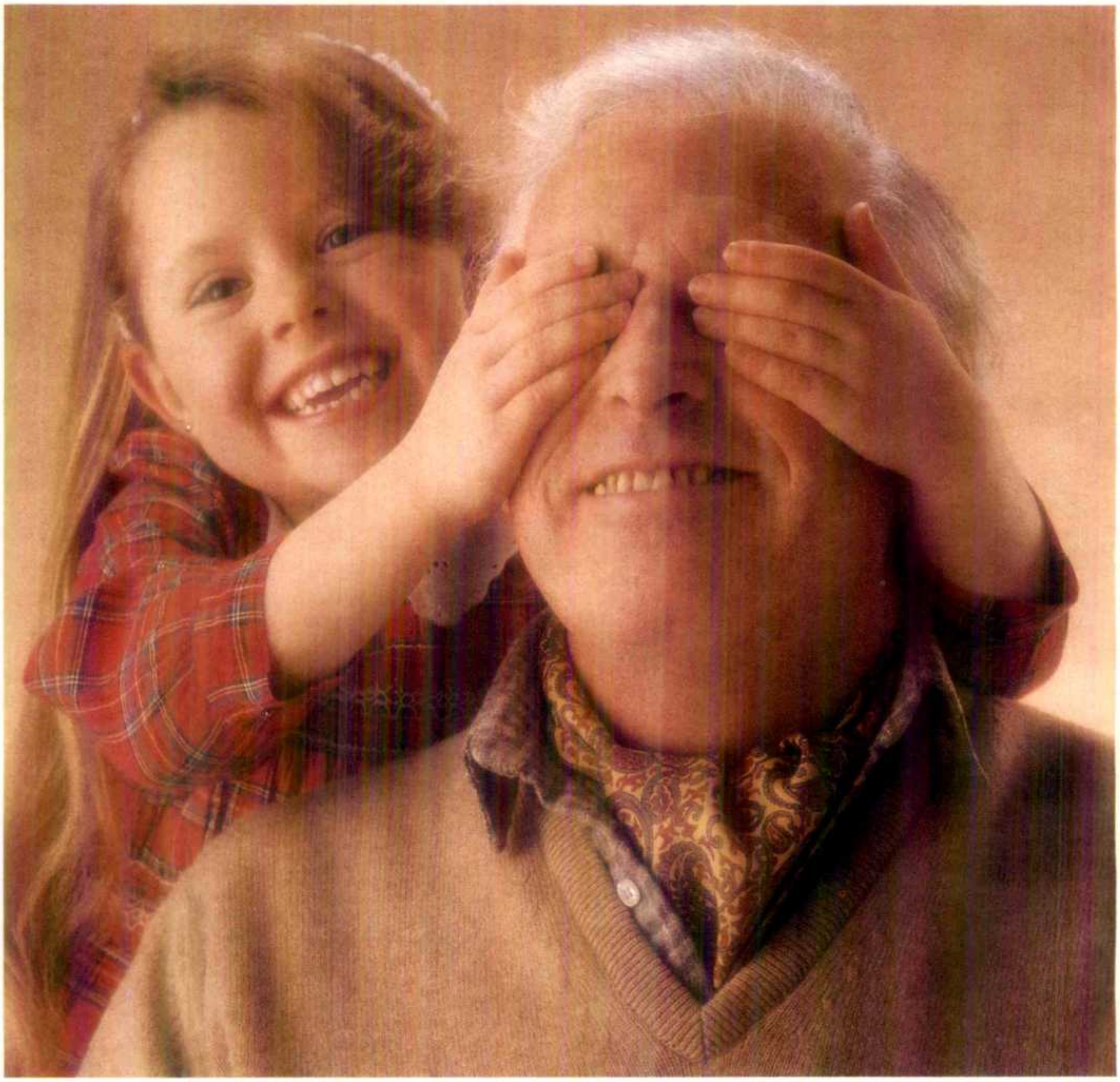

In a recent study[1], 57 prostate cancer patients were invited to participate in choosing their treatment. All were informed that the two treatments available, sub-capsular orchidectomy or 'Zoladex', were similar in efficacy and side effects. 49 of the patients (86%) opted for 'Zoladex'.

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2. Peeling W B. ibid: 27-46.

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Br. J. Surg. 1989, Vol. 76, March, 211–212

Editorial process at The British Journal of Surgery

Now that I am no longer responsible for *The British Journal of Surgery* policy and have seen a new management take over, I feel it might be helpful for readers and potential, or even experienced, authors to know how we have run the Journal over the past years—a pattern that will probably persist at least for the moment.

First I should make it absolutely clear that the Editors are completely independent. There is an Editorial Committee but its work is largely related to overall policy and financial matters. The Editorial Committee also maintains a healthy interest in the sales of the Journal, so providing a goad to the publishers. Beyond this, the Chairman and his committee vest all day-to-day decisions in the Editors and are there to back them up if problems occur.

These things having been established, how is an individual paper dealt with? When a paper reaches the Editorial Office it is allocated a number for identification purposes which follows it through the rest of its editorial life or death. An editorial decision is then taken about whether or not it should be subject to peer review. At this stage the Editors are entitled to say if the paper is in no way suitable for the Journal; they do this rarely and sometimes I wish that they would more often follow the *Lancet*'s policy of making radical and arbitrary judgements. However, editors are usually cautious people and I cannot blame them for sending most of the papers, in the increasingly specialized fields of surgery, out to referees.

The process of 'peer review' has been debated endlessly and is superbly reviewed by Stephen Lock in his Rock Carling lecture[1]. This instrument is fallible but it is the best we have. Nevertheless it can be made more realistic (if not more precise) by two manoeuvres, both of which are part of the editorial process at *The British Journal of Surgery* . First we send the manuscript to two independent referees; this may give the Editors two biased views. Of more significance is the fact that we send each referee's observations to his opposite number, so discouraging him from careless or outrageous statements that might offend his colleague. Second, we insist that the referee's report should be couched in terms that can be transmitted to the author. We have no objective data about the effect of these measures but we feel that both tend to make the referee more responsible and accountable. Certainly I personally have found that the knowledge that my observations will be transmitted both to my peer colleague and to the authors has concentrated my mind. Furthermore, it has made me refrain from making outright scurrilous criticism, though it has also inhibited the free flow of my invective in a way that I sometimes regret. The two referees' reports are then returned to the Editors. Usually the referees agree and the concordance rate over whether to publish or not is around 60 per cent. The editors are then faced with making a value judgement which embraces at least three things. Is the paper a real contribution to the science and practice of surgery? If so, it ought to be published. Given this, is there room for the paper in the Journal, which is restricted to a certain size by the economics of publishing? Finally, if neither of the preceding criteria apply, how can the Editor best tell the author(s) that the work is at present not suitable for publication in the Journal? There is a difficult balance on the one hand between saying outright that the work is bad and on the other hand that it is not suitable for the audience that the Editors feel is 'out there' waiting for the next issue of the Journal. Here there are no decision rules to choose decision rules.

Going back to the distinction between what is publishable and what can be published, it is often confusing for authors to receive an encouraging referee's report and at the same time a rejection from the editor. Could I just emphasize that journals cannot lose money if they are to survive; in consequence there is a fine balance between the production costs, the advertising revenue, the subscription base and the size of the Journal in terms of editorial pages. We always wish to expand but the laws of the market-place govern our ability to do so.

Given that a paper has survived all these hurdles, there is yet the matter of sub-editing. Few authors seem to realize that their manuscript is often riddled with spelling errors, grammatical infelicities and flights of fancy that fly in the face of logic and clear exposition. Referees often help us in this task (and I have had my own

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seemingly pellucid writing savaged and salvaged quite justifiably in this way), but there remains a burden on the editorial staff which often results in a final form of which the authors are proud even though they owe it all to hidden editing. There are two components to this sub-editorial task. Firstly, making sure that there are no professional uncertainties; here we must rely, for the most part, on our referees, but from time to time members of the Editorial Committee (including the Chairman) are asked to make a final Solomonic judgement. Secondly, there is the tedious business of checking references and referring back to the author(s) over obscure matters and minor points. The Editorial Office finds itself doing a great deal of chasing after missing items of information which could be reduced if authors were more careful with their manuscripts. There is also the possibility of being chased by indignant authors who feel that they are not getting a square deal, but thankfully this is uncommon.

Once a paper is through this phase there remains the delay between acceptance in principle, acceptance in fact (when all errors and problems are eliminated), and publication time. The last is determined by the following: pressures of priority—a new and unique observation is likely to be published ahead of more mundane matters (as viewed by the Editors of course); the desire to associate papers on a similar or related subject, so building up an issue of the Journal that is seen to represent a theme; and the parallel aims that the Journal must pursue. Among the latter are the publication of the Abstracts of the Surgical Research Society, a special issue for the Association of Surgeons, and the legitimate demands of a vigorous correspondence column.

Thought must be spared, therefore, for the difficult task the Editors and the Editorial Committee have in order to meet these diverse needs. *The British Journal of Surgery* is here to serve surgery in general and British surgery in particular. If its balancing act does not please everyone all the time, this is because the task is so complex.

H. A. F. Dudley

Past Chairman British Journal of Surgery Society
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1. Lock S. *A Difficult Balance*. London: Nuffield Provincial Hospitals Trust, 1985.

Br. J. Surg. 1989, Vol. 76, March, 213–214

Intrahepatic stones

In an article entitled 'Common Duct Stones of Liver Origin'[1], Digby drew attention to the common occurrence of stone formation in the intrahepatic bile ducts among the Hong Kong Chinese. It is now a recognized disease entity with the highest incidence found in Taiwan, Hong Kong and the southern part of China, followed by Japan, Korea and Singapore. In Taiwan, where the incidence is the highest, 30 per cent of all patients suffering from gallstone disease have intrahepatic stones[2].

Intrahepatic stones are in the most part made of calcium bilirubinate. Stones are formed as a result of infection of the intrahepatic ducts by enteric bacteria, many species of which produce a large amount of the enzyme β-glucuronidase. The enzyme deconjugates bilirubin diglucuronide in the bile. The deconjugated bilirubin combines with calcium ions to form insoluble calcium bilirubinate[3]. Based on the similarity between the bacteria found in the intrahepatic stones and the gut flora, the source of the bacteria is probably the gut. The route of transmission is uncertain, and it is not known whether the bile ducts or the liver of patients suffering from this disease have a lower resistance to bacterial colonization.

Patients usually present with symptoms of cholangitis, namely fever, right upper quadrant tenderness and jaundice. The symptoms may be mild and non-specific or severe, with mental confusion and shock. After preliminary blood tests to confirm the presence of infection and obstructive jaundice, ultrasonography of the liver and the gallbladder is performed. In expert hands, 90 per cent of the intrahepatic stones can be detected by ultrasound. If the diagnosis is confirmed or strongly suspected on clinical grounds, conservative treatment, consisting of nothing by mouth, intravenous fluids and antibiotics, is started.

A better knowledge of the bacterial flora involved and the availability of potent antibiotics in the last few years have greatly improved the outcome for patients with intrahepatic stones. In the past, up to 50 per cent of patients did not respond to conservative treatment and had to be operated on as emergencies. Emergency operations carried a high risk of mortality (15 per cent). Furthermore, because of the precarious condition of the patients, the operative procedures were temporizing and frequently inadequate. Even if the patients' vital signs were stable during the operation, surgeons were frequently unable to perform definitive procedures because of insufficient knowledge of the location of stones and the presence of biliary strictures. Thus, with few exceptions, patients undergoing emergency operations had retained stones or unrelieved strictures or both. Before the development of postoperative choledochoscopy, some patients with retained stones and strictures were subjected to second operations while others were left untreated. Because of this, the incidence of recurrent symptoms was high.

Today, less than 15 per cent of patients require urgent intervention owing to antibiotic treatment failure. The patients who recover undergo thorough investigations including repeated ultrasonography, endoscopic retrograde cholangiopancreatography (ERCP) and occasionally both ERCP and percutaneous transhepatic cholangiography. The surgeon, armed with complete information about the biliary system, is then able to plan and perform more definitive operations.

A definitive operation starts with a routine common bile duct exploration, during which flexible choledochoscopy is performed. All the segmental bile ducts are examined. The sites of stones and strictures as shown by preoperative studies are confirmed. If the stones and strictures are localized to a segment or lobe of the liver and the involved part of the liver is atrophic, liver resection is performed[4]. In this setting, operative mortality of liver resection is only 2 per cent and the long-term results are excellent. If liver resection is not indicated, stone forceps and irrigation are first used to extract easily removable stones. Further stones are retrieved with wire baskets and biliary balloon catheters under choledochoscopic guidance[5]. Large stones impacted in the right or left hepatic ducts or at their confluence are removed by extending the choledochotomy into the hepatic ducts. Large stones in the segmental ducts are first broken up with electrohydraulic shock waves. The electrode can be introduced through the working channel of the flexible choledochoscope, taking care to extend the tip at least 1·5 cm beyond the choledochoscope. The fragments are then either flushed out or removed with basket retrievers. Occasionally, it is not possible to remove all stones because of their large number and peripheral location[5]. Some stones may be left behind to be removed by postoperative flexible choledochoscopy[6].

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Treatment of biliary strictures requires preoperative identification and planning. Strictures associated with intrahepatic stones can be found intrahepatically or extrahepatically. Extrahepatic strictures are treated by sphincteroplasties if they are located in the ampullary region. Higher extrahepatic strictures are treated by hepaticojejunostomies. Intrahepatic strictures are treated by biliary–enteric anastomosis to segmental bile ducts. The left hepatic duct is most frequently involved. Bypass using the segment III duct and the round ligamental approach[7] is the best treatment for left hepatic duct strictures. Stones can be removed directly from the dilated segmental ducts when they are opened for biliary–enteric anastomosis. Occasionally, intrahepatic strictures are diaphragm-like, and are located close to the right and left hepatic duct confluence. In these cases, the strictures are exposed by extending the choledochotomy. The diaphragms are partially excised and the ducts are reconstructed by a procedure similar to the sphincteroplasty used for widening the sphincter of Oddi.

Postoperative flexible choledochoscopy is used to remove any stones which are left behind or missed at operation. This procedure is performed via the T tube tract about 6 weeks postoperatively. About 85 per cent of the intrahepatic stones shown by postoperative cholangiography can be successfully removed[6]. With such advances in stone retrieval techniques, the ultimate retained stone rate has been reduced from approximately 50 per cent to about 5 per cent. The reduced incidence of retained stones combined with adequate relief of biliary strictures should reduce the rate of recurrent symptoms, which amounts to about 25 per cent over 5 years[8]. In our preliminary review of patients treated recently, the symptomatic recurrence rate is reduced to about 5 per cent; however, the median follow-up is still short (2 years) and long-term results are awaited.

Several controversial points concerning the treatment of intrahepatic stones remain to be settled. Intrahepatic stones have been removed by non-operative procedures and, among them, percutaneous transhepatic choledochoscopy (PTCS) is the most successful. Whether this should be done instead of surgery is not clear at present. As about 35 per cent of the patients with intrahepatic stones also have significant strictures in major bile ducts, and 40 per cent also have gallbladder stones, it would appear that PTCS is not suitable for the majority of patients. Another unanswered question is whether emergency surgery or endoscopic papillotomy combined with nasobiliary drainage should be performed in patients who do not respond to conservative treatment. The latter approach is preferred if it is effective in relieving biliary obstruction and infection caused by intrahepatic stones as it will allow patients to undergo operation in safer circumstances and after proper investigation. Many stone dissolution and fragmentation techniques have also been developed and applied to intrahepatic stones. Ethylenediaminetetra-acetic acid dissolution, and laser or ultrasound fragmentation are some examples. Which technique is superior and which should be used in a given situation are areas which deserve further study.

T. K. Choi

University of Hong Kong
Queen Mary Hospital
Hong Kong

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Mortality and perforated peptic ulcer: a case for risk stratification in elderly patients

In a consecutive series of 284 patients with a perforated peptic ulcer (229 pyloroduodenal, 55 gastric) there was a 26 per cent hospital mortality rate, and patients aged ⩾70 years ($n=176$) *had a significantly higher mortality rate (34 per cent) than patients aged <70 years (14 per cent,* $P<0{\cdot}001$*). Multiple clinical variables were significantly more common in the elderly group of patients (65 per cent), in those having non-steroidal anti-inflammatory drugs or steroid therapy (56 per cent), in patients where there is an absence of a previous dyspeptic history (69 per cent), and when risk factors such as delayed presentation (33 per cent) and the presence of shock on admission to hospital (27 per cent) are present. Definitive operations (vagotomy or gastrectomy) had an increased mortality rate in the elderly* ($P=0{\cdot}018$)*. Risk scores based upon the presence of shock, delayed presentation or concurrent medical illness could have predicted 87 per cent of postoperative deaths in elderly subjects, and it is suggested that risk stratification and greater caution in the use of definitive operations for perforated ulcer may result in a reduction in the high mortality rate in elderly subjects.*

Keywords: Perforated peptic ulcer, geriatric

T. T. Irvin

*Department of Surgery, Level 4,
Royal Devon and Exeter Hospital
(Wonford), Barrack Road, Exeter,
EX2 5DW, UK
Correspondence to:* Mr T. T. Irvin

There has been a dramatic reduction in the incidence of elective operations for chronic peptic ulceration during the last decade following the introduction of the H_2-receptor antagonist drugs[1–4]. There has also been a reduction in the incidence of perforated peptic ulcer[5] but there is reason to believe that the mortality rate as a result of this complication may be increasing. Many perforations occur in elderly subjects with acute rather than chronic peptic ulcers and mortality rates of 18–48 per cent have been reported[5–7].

We have reviewed our recent experience of 284 consecutive patients with a perforated peptic ulcer, with particular reference to the factors determining the outcome in elderly subjects.

Patients and methods

The case records of 284 patients with a perforated peptic ulcer admitted to the surgical units of the Royal Devon and Exeter Hospital during the period 1979–86 were reviewed. The patients were admitted under the care of five consultant surgeons and the diagnosis was confirmed by operation in 265 patients, by radiology in three and at autopsy in 16. The study included an analysis of the clinical features of the patients on admission, the incidence of adverse prognostic or risk factors[8,9], the methods of surgical treatment, the causes of death, and the 30-day hospital mortality rate. For the purpose of the study the patients were divided into two groups according to their age at presentation: a group of 176 patients aged ⩾70 years, and a group of 108 patients aged <70 years.

The risk factors or adverse prognostic factors examined in this study were based on the criteria of Boey *et al.*[9] and included the presence of shock on admission to hospital (a documented systolic blood pressure <100 mmHg), delayed presentation (>24 h after perforation), and serious concurrent medical illness. In most cases the medical illnesses had required previous attendance at hospital on at least one occasion, and they included major chronic cardiovascular or respiratory disease, diabetes, renal failure, hepatic insufficiency, and various types of disseminated malignancy.

The results were subjected to statistical analysis using the χ^2 test and Fisher's exact test.

Results

The majority of patients were elderly. The average age was 70 years (range 19–98), and the male:female ratio was 1:1·1. Pyloroduodenal ulcers occurred in 229 patients (81 per cent) and gastric ulcers in 55 (19 per cent). A previous dyspeptic history >3 months was elicited in 109 patients (38 per cent), and 124 patients (44 per cent) were receiving either non-steroidal anti-inflammatory drugs (NSAIDs) or systemic corticosteroids. Shock, delayed presentation, and concurrent medical illness occurred in 21, 26, and 30 per cent of cases respectively.

Clinical features of the two groups of patients (Table 1)

The average age of the elderly group of patients was 80 years compared with an average age of 55 years in the group aged <70

Table 1 *Clinical features of the two groups of patients*

	Age ⩾70 years	Age <70 years
No. of patients	176	108
Mean age (years)	80	55
Range	70–98	19–69
Sex:		
Male	65 (37)	72 (67)
Female	111 (63)*	36 (33)
Ulcers:		
Pyloroduodenal	141 (80)	88 (81)
Gastric	35 (20)	20 (19)
Dyspepsia >3 months	54 (31)	55 (51)†
NSAIDs or steroid therapy	98 (56)*	26 (24)
Risk factors		
Shocked on admission	47 (27)‡	13 (12)
Delayed presentation (>24 h)	58 (33)*	16 (15)
Medical illness	59 (34)	25 (23)
Risk scores		
No. of cases with positive score	117 (67)*	39 (36)
One factor	78 (44)	27 (25)
Two factors	31 (18)	9 (8)
Three factors	8 (5)	3 (3)

Figures in parentheses are percentages. * $P<0{\cdot}001$, ‡ $P<0{\cdot}01$: significantly higher incidence in patients aged ⩾70 years; † $P<0{\cdot}001$: significantly higher incidence in patients aged <70 years; NSAIDs, non-steroidal anti-inflammatory drugs

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Table 2 *Methods of treatment in the two groups of patients*

	Age ≥70 years	Age <70 years
No operation	14 (8)	5 (5)
Suture/patch	54 (31)	24 (22)
Vagotomy and drainage	90 (51)	69 (64)
Gastrectomy	18 (10)	10 (9)

Figures in parentheses are percentages

Table 3 *Comparison of mortality rates in the two groups of patients*

	Age ≥70 years		Age <70 years	
	No. of cases	No. of deaths	No. of cases	No. of deaths
All patients	176	59 (34)*	108	15 (14)
Postoperative	162	47 (29)*	103	11 (11)
Operations				
Suture	54	23 (43)†	24	9 (38)‡
Vagotomy	90	19 (21)§	69	2 (3)
Gastrectomy	18	5 (28)§	10	–
Ulcers (operated)				
Pyloroduodenal	128	33 (26)‖	86	11 (13)
Gastric	34	14 (41)¶	17	–

Figures in parentheses are percentages. * $P<0.001$: significantly higher mortality rate in patients aged ≥70 years; † $P<0.01$, ‡ $P=0.0001$: significantly higher mortality rate after suture compared with definitive operations; § $P=0.018$: significantly higher morality rate after definitive operations in patients aged ≥70 years; ‖ $P<0.05$, ¶ $P=0.001$: significantly higher mortality rate in patients aged ≥70 years

years, and the elderly group included a significantly higher proportion of women, patients receiving treatment with NSAIDs or steroids ($P<0.001$), and a significantly higher incidence of risk factors such as shock ($P<0.01$) and delayed presentation ($P<0.001$).

Risk scores were calculated for the two groups based on the presence of shock, delayed presentation or concurrent medical illness, and the elderly group had a significantly higher incidence of positive risk scores ($P<0.001$).

Methods of treatment (Table 2)

Nine patients (all aged ≥70 years) were moribund on admission to hospital and died within a few hours. Ten patients were treated conservatively: in three cases (two ≥70 years, one <70 years) because they were judged to have a localized perforation, and in seven cases (three ≥70 years, four <70 years) because they were judged to be unfit for any surgical procedure.

Simple suture of the perforation with an omental patch was performed in 28 per cent, and there was a slightly higher incidence of suture operations in the elderly. All patients received H_2-receptor antagonists after these procedures, and 16 patients with gastric ulcers treated by suture either had a biopsy or excision of the ulcer for histological confirmation of peptic aetiology.

More than 70 per cent of perforations were treated by a definitive procedure, usually a truncal vagotomy and drainage procedure, and there was a significantly higher incidence of definitive procedures in patients aged <70 years ($P<0.05$).

The operations were performed by five consultant surgeons and junior staff of registrar or senior registrar status. Ninety per cent of the operations were performed by the junior staff, and there was a similar distribution of junior and senior surgeons involved in the treatment of both groups of patients. Only 13 per cent of the operations were performed during the night (midnight–09.00 hours), and the highest proportion (44 per cent) occurred in the evening (17.00–24.00 hours).

Mortality (Tables 3 *and* 4)

The overall hospital mortality rate was 26 per cent, and 58 postoperative deaths resulted in a perioperative mortality rate of 22 per cent. Seven of the ten patients treated conservatively failed to survive.

The mortality from perforated peptic ulcer was clearly age-related (*Figure 1*), and there was a significantly higher mortality rate in patients aged ≥ 70 years (34 per cent overall, and 29 per cent postoperatively). Comparison of the two groups of patients (*Table 3*) revealed a significantly higher mortality rate after simple suture compared with definitive procedures (vagotomy or gastrectomy) in both groups but patients aged ≥70 years had a significantly higher mortality rate after definitive operations than those aged <70 years ($P=0.018$): definitive procedures in patients aged <70 years resulted in a mortality rate of only 3 per cent. The higher mortality rate in the elderly occurred irrespective of ulcer type although there was a particularly high rate (41 per cent) after operations for gastric ulcer.

The majority of deaths after ulcer surgery were related to coexisting cardiovascular or chronic respiratory diseases (*Table 4*) but there was a high incidence of fatal pulmonary embolism in the elderly (6 per cent after simple suture and 2 per cent after definitive operations), and a 6 per cent incidence

Table 4 *Causes of death after simple suture or definitive procedures (vagotomy or gastrectomy) in the two groups of patients*

	Age ≥70 years		Age <70 years	
	Simple suture	Definitive procedure	Simple suture	Definitive procedure
Cardiac failure/infarction	11	10	2	–
Respiratory failure	5	3	2	2
Cerebrovascular accident	–	2	2	–
Renal failure	–	–	1	–
Hepatic failure	–	–	1	–
Pulmonary embolism	3	2	1	–
Sepsis	1	1	–	–
Gastrointestinal bleed	1	–	–	–
Burst abdomen	–	2	–	–
Fistula/reperforation	2	4	–	–

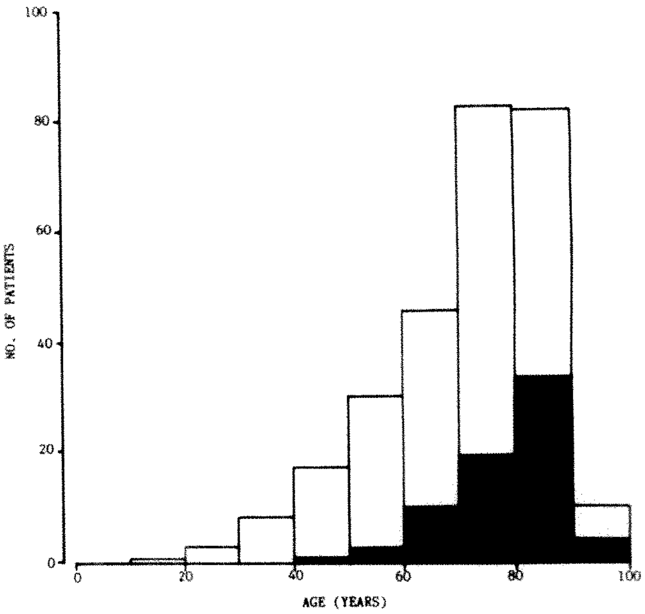

Figure 1 *Age of patients and associated mortality rate.* ■, *Deaths*

Table 5 *Comparison of mortality rates and risk factors in patients undergoing surgical treatment in the two groups*

	Age ≥70 years		Age <70 years	
	No. of cases	No. of deaths	No. of cases	No. of deaths
Risk factors				
Shocked on admission	41	28 (68)*	11	4 (36)
Delayed presentation	57	20 (35)	14	1 (7)
Medical illness	50	20 (40)†	20	10 (50)‡
Risk scores				
0	53	6 (11)	70	2 (3)
1	75	20 (27)	23	4 (17)
2	29	16 (55)	8	3 (38)
3	5	5 (100)	2	2 (100)

Figures in parentheses are percentages. * $P<0\cdot001$, † $P<0\cdot05$: shock and medical illness significantly related to mortality rate in patients aged ≥70 years; ‡ $P<0\cdot001$: medical illness significantly related to mortality rate in patients aged <70 years

of potentially avoidable fatal complications after definitive operations in this group, including burst abdomen and disruption of gastrointestinal suture lines.

The majority of deaths and complications were related to the large number of operations performed by surgeons in training, but the mortality rate (20 per cent) was actually slightly less than that encountered by consultant surgeons (24 per cent). However, a higher proportion of the consultant operations were definitive procedures for perforated gastric ulcers.

Risk factors (Table 5)

The association between risk factors and mortality has been studied only in the 265 patients who were judged to be candidates for a surgical operation. Moribund patients and those considered totally unfit for a general anaesthetic have been excluded from the analysis.

The presence of shock on admission (systolic pressure <100 mmHg) and concurrent medical illness were significant independent prognostic factors in patients aged ≥70 years but only concurrent medical illness was significantly related to the mortality in patients aged <70 years. Delayed presentation (>24 h) was not a significant independent prognostic factor in either group. Certain risk factors (concurrent medical illness and delayed presentation) were significantly more common in patients treated by simple suture ($P<0\cdot01$), and this factor may account for the higher mortality rate after suture operations.

Risk scores had significant value in the prediction of perioperative mortality, and a scoring system utilizing three prognostic variables (shock, delayed presentation, and concurrent medical illness) had greater sensitivity than a system based on two factors (shock and medical illness). The three-factor system predicted 41 of 47 deaths in patients aged ≥70 years (87 per cent sensitivity) and 9 of 11 deaths in patients aged <70 years (82 per cent sensitivity). However, the system had rather less specificity (41 per cent in patients aged ≥70 years and 74 per cent in patients aged <70 years). The two-factor system had a 74 per cent sensitivity and 60 per cent specificity in patients aged ≥70 years, and a 64 per cent sensitivity and 77 per cent specificity in patients aged <70 years.

Discussion

In a review of perforated duodenal ulcer 10 years ago, Johnston[10] stated that there was an average perioperative mortality rate of 7 per cent, and he made a plea for the greater use of definitive operations in selected patients with chronic ulcers. However, there is evidence that the epidemiology and mortality rate in patients with perforated peptic ulcer are changing. In a review[5] of perforated ulcers (duodenal and gastric) presenting in Oxford, UK during the period 1965–82 it was found that the average age of men with duodenal ulcer was increasing (59 years in the period 1977–82), that there was an increasing incidence of perforation in women, and that the majority of the patients had acute ulcers. The overall mortality rate for the period 1977–82 was 13 per cent but patients aged >70 years had a mortality rate of 30 per cent. Other reviews of perforated peptic ulcer in the USA[7] and in the UK[6] have reported mortality rates of 18–48 per cent in the elderly.

In the present study the average age of the patients was 70 years, and the overall mortality rate was 26 per cent. The mortality was clearly age-related: patients aged ≥70 years had a mortality rate of 34 per cent, and in those aged <70 years it was 14 per cent. Studies of the group aged ≥70 years showed that the majority of patients were women, more than half were receiving NSAIDs or systemic steroids, and few (31 per cent) had any significant dyspeptic history.

It is perhaps surprising, therefore, that the majority of patients had a definitive operation, usually a vagotomy and pyloroplasty for pyloroduodenal perforation. It is not possible in this retrospective analysis to elicit the factors that determined the choice of operation in most cases, although it appears that the use of definitive surgery was governed by the appearance of the ulcer at operation rather than by the dyspeptic history.

Retrospective studies of the clinical variables which may be associated with the mortality of perforated peptic ulcer have suggested that the risk factors include shock, advanced age, delayed presentation, and significant peritoneal contamination[11–14]. However, in a prospective study of perforated duodenal ulcers presenting in Hong Kong, Boey *et al.*[8] found that the risk factors which had independent significance in relation to perioperative mortality were preoperative shock (blood pressure <100 mmHg), concurrent medical illness, and long-standing perforation (delayed presentation). The significance of these risk factors was validated in a second prospective study[9] and it was possible to predict the mortality risk in patients undergoing surgery by stratification of the risk factors. A scoring system utilizing preoperative shock (blood pressure <100 mmHg), concurrent medical illness, and delayed presentation (>24 h) had 100 per cent sensitivity and a false-positive error rate of 50 per cent. Patients with one, two, or three risk factors had mortality rates of 10, 46, and 100 per cent respectively. On the basis of these findings the authors suggested that risk stratification should be used in the selection of patients for definitive duodenal ulcer surgery, and that such operations should be performed only in good-risk patients.

We have examined the same risk factors in this retrospective analysis of perforated peptic ulcer in Exeter. The patients are by no means comparable with those studied in Hong Kong[9] where the average age was 51 years and the male:female ratio was 3·6:1. Moreover, the Hong Kong study excluded patients with gastric ulcers. These factors and the inevitable limitations of a retrospective analysis may explain some of the differences in the results of the two studies. In the Exeter patients undergoing surgical operations, preoperative shock was a significant independent prognostic factor only in patients aged ≥70 years, and delayed presentation did not have independent prognostic significance in either of the groups studied. Clearly, a retrospective assessment of shock based on a systolic blood pressure <100 mmHg is questionable, but this parameter was used in the Hong Kong studies. We have no comparative information regarding the adequacy of resuscitative procedures for shock in Exeter and Hong Kong.

Concurrent medical illness was a significant factor at any age but it is unlikely that the medical illnesses were identical in Exeter and in Hong Kong. Unfortunately, the Hong Kong study[9] did not describe these illnesses although the earlier report from the same department[8] listed cardiorespiratory disorders, hepatic precoma, diabetes and renal failure as concurrent medical conditions. All of these were included in the Exeter study together with various types of disseminated malignancy.

In this retrospective assessment, the method of risk stratification also enabled the prediction of mortality in patients undergoing surgery in Exeter, although the system was not so effective as in Hong Kong: the scoring system had an 87 per cent sensitivity and 41 per cent specificity in patients aged $\geqslant 70$ years, and an 82 per cent sensitivity and 74 per cent specificity in patients aged <70 years. Risk scores of 1, 2, or 3 were associated with mortality rates of 27, 55, and 100 per cent in patients aged $\geqslant 70$ years, and the corresponding mortality rates for patients aged <70 years were 17, 38, and 100 per cent.

These results suggest that some form of risk stratification should be used in the selection of surgical procedures for patients presenting with perforated peptic ulcers, particularly in the large numbers of elderly subjects who have an increased mortality risk. It has yet to be established that such a policy will save lives since a reduction in the number of definitive procedures might simply result in a further increase in the mortality rate associated with simple suture. Moreover, as Johnston[10] has pointed out, simple suture of duodenal ulcers is not devoid of complications. Nevertheless, we feel that there is a strong case for greater caution in the use of definitive procedures in elderly subjects since the majority of patients have acute rather than chronic ulcers, and our experience suggests that the risks of definitive operations are higher in the elderly.

The principal concern regarding the use of suture operations for perforated duodenal ulcer is that a proportion of patients treated by this method may have continuing problems with ulceration either immediately or within a few months of surgery, but this concern has been reduced by the finding that the use of the histamine antagonist drugs largely prevents such problems[15].

Recent reports of the treatment of patients with perforated duodenal ulcer in Ireland[16] and in Hong Kong[17] have suggested that 70–75 per cent of cases may be successfully managed by conservative non-operative treatment using nasogastric intubation and histamine antagonist drugs. However, it should be noted that the majority of patients treated in these studies were not elderly, and the safety of a non-operative treatment policy for perforated duodenal ulcer in the elderly has yet to be established.

The smaller number of patients presenting with perforated gastric ulcers have a worse prognosis than those presenting with duodenal ulcers. In this study the majority of such patients were aged $\geqslant 70$ years, and there was a 41 per cent perioperative mortality. Some of these ulcers are giant lesions and nothing short of a definitive operation (usually a gastrectomy) will be adequate treatment. However, most ulcers are small acute lesions, and we believe that the same rules of risk stratification should apply in these patients. Simple suture is adequate treatment for such ulcers provided that biopsy material is obtained for histological examination.

The risks attached to surgical operations for perforated peptic ulcer may be reduced by greater involvement of consultant surgeons in the management of such cases although few deaths in the present study were attributed to iatrogenic or potentially avoidable complications. The high mortality rates encountered in Exeter and elsewhere in the UK[5,6] surely justify such attention and a regular audit of the outcome of perforated peptic ulcer.

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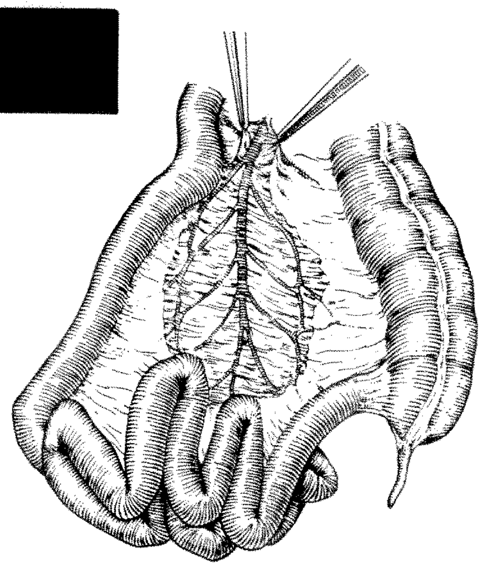

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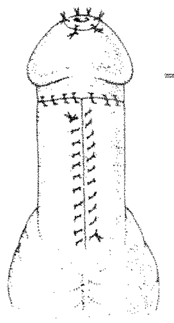

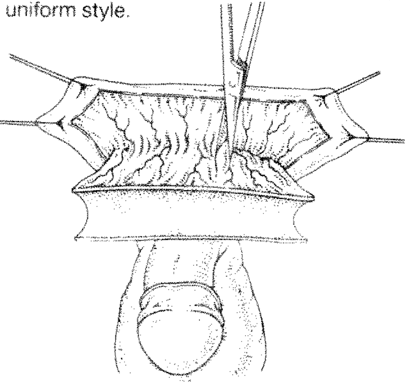

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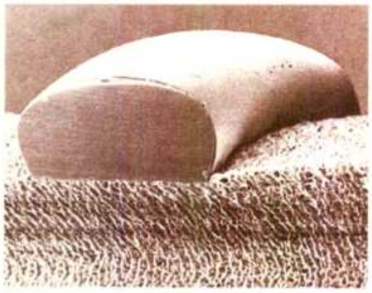

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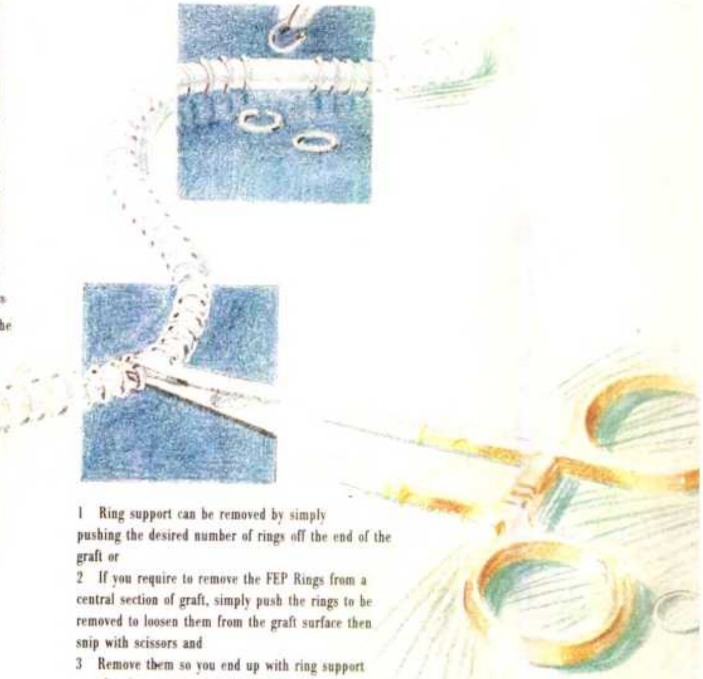

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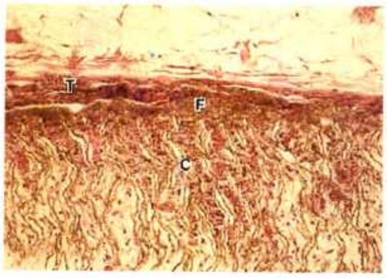

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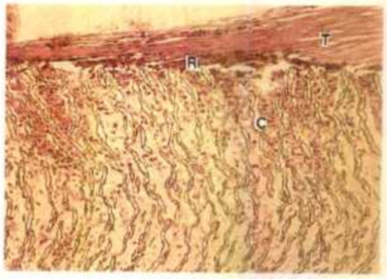

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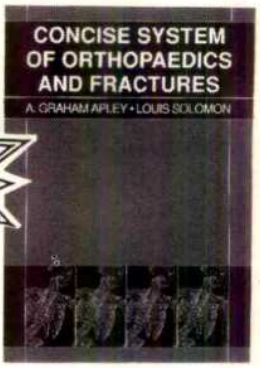
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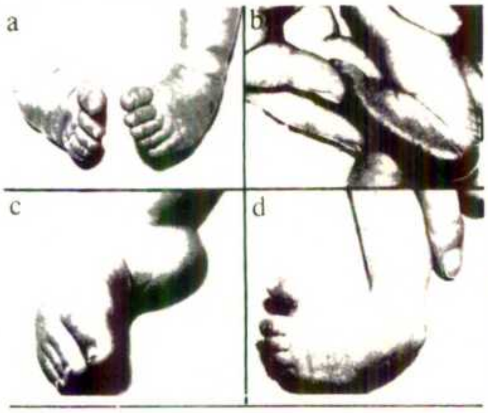

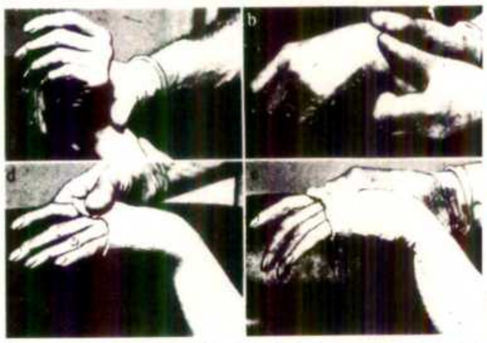

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Endoscopic haemostasis for non-variceal upper gastrointestinal haemorrhage

R. J. C. Steele

Department of Surgery, University Medical Buildings, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZB, UK

Correspondence to:
Mr R. J. C. Steele

Endoscopic haemostasis can be effective in non-variceal upper gastrointestinal haemorrhage, and should be regarded as potential front-line treatment. Diverse methods are available, and although no single technique has become firmly established, current evidence favours thermal coagulation and injection therapy.

Keywords: Endoscopy, gastrointestinal haemorrhage, haemostasis

Sclerotherapy is well established in the treatment of oesophageal varices[1], but in no sense can it be regarded as curative[2,3]. Endoscopic haemostasis for non-variceal bleeding, however, is more satisfactory as it represents only the first step in the management of a disease which is usually amenable to treatment. Thus, if haemorrhage from a peptic ulcer is controlled by non-operative means, then subsequent elective medical or surgical therapy can usually effect a cure without significant hazard. Furthermore, bleeding from lesions such as Mallory–Weiss tears, arteriovenous malformations and even cancers can be controlled by endoscopic means.

Why, then, is endoscopic haemostasis not more widely practised? Paradoxically, of all the techniques currently available that which was first introduced and which has undoubtedly received the most attention is also the most expensive, complex and difficult to learn. Since the introduction of the therapeutic laser[4], there have been at least 11 controlled trials of endoscopic laser photocoagulation for upper gastrointestinal bleeding[5]. Despite the fact that only six of these have demonstrated any benefit at all, a tacit assumption that laser equipment represents a *sine qua non* may have inhibited many centres from attempting to develop therapeutic endoscopy for non-variceal bleeding. It is, however, becoming increasingly clear that simpler and cheaper techniques are probably as effective as laser therapy, and may indeed have distinct advantages.

The aim of this article is to review and compare the available methods in order to assess the efficacy and applicability of endoscopic haemostasis as it stands today.

The problem

Fibreoptic endoscopy is the method of choice for ascertaining the precise diagnosis in acute upper gastrointestinal haemorrhage[6], and it is known that early investigation is more likely to be helpful than endoscopy which is delayed for 48 h or more[7]. Nevertheless randomized trials have failed to demonstrate any improvement in mortality resulting from routine early endoscopy[6,8], leading to the suggestion that it should be abandoned. Counter to this argument is the finding from Australia that setting up a specialized unit which emphasizes prompt endoscopy has reduced mortality from acute upper gastrointestinal bleeding from 15 to 6 per cent within a few years[9].

These points, although noteworthy, refer only to diagnostic endoscopy, and the emergence of therapeutic manoeuvres has added a further dimension. One of the problems in demonstrating a reduction in mortality for gastrointestinal haemorrhage is the fact that death rates should now be less than 10 per cent, and it would therefore require a trial with very large numbers of patients to demonstrate a significant effect resulting from a specific treatment[10]. Accordingly, another end point is necessary in order to interpret the value of any method, and the most obvious is the need for emergency surgery. Elective surgery for peptic ulcer has been extremely safe for some years now, with many series reporting no mortality[11–13]. Urgent operation for bleeding, however, can be associated with a mortality rate of around 20 per cent[14]. It is therefore reasonable to assume that any significant reduction in emergency surgery would eventually translate into a lowering of mortality rate, to say nothing of perioperative morbidity.

Even a reduction in the number of emergency operations, however, is difficult to demonstrate unless the patients studied are at high risk of continued or further bleeding from the lesion which is to be treated endoscopically. Active haemorrhage would seem to place patients in this category but, as over 70 per cent of all acute upper gastrointestinal bleeding episodes stop spontaneously[15], fortuitous endoscopic visualization of actual bleeding cannot be regarded as an absolute indication for intervention. Moreover, it is now evident that a 'visible' or exposed vessel in an ulcer base is a powerful predictor of rebleeding[16–18] and represents as clear an indication for treatment as does fresh haemorrhage.

It is therefore important that any method of endoscopic haemostasis be subjected to randomized trials in which the control patients are treated conservatively until they fulfil criteria which are not based on endoscopic appearances. Indeed, when adequately documented studies of this type are combined, it would appear that untreated patients with arterial bleeding, non-arterial bleeding and visible vessels come to emergency surgery in only 59, 24 and 38 per cent of cases respectively (*Table 1*). It should also be stressed, however, that the endoscopic appearance of an ulcer is not the only predictive factor. Two recent studies have highlighted the unfavourable prognostic significance of hypovolaemic shock[19,20], and ulcer position is similarly relevant, with rebleeding being more common from lesions situated in the posteroinferior duodenum or high in the lesser curve of the stomach[21].

Endoscopic haemostasis, then, is most appropriate for actively bleeding lesions or visible vessels, and the presence of shock and ulcer position may also help in the selection of patients for treatment. In the following section each technique will be described, and its efficacy will be critically assessed with the emphasis on controlled trials. An attempt will then be made to compare the different approaches using those reports which contain adequate data.

The methods

Different methods of endoscopic haemostasis are legion but the most firmly established are those employing thermal coagulation and injection. The commonly used thermal methods consist of laser photocoagulation, monopolar or bipolar electrocoagulation and the direct application of heat using a 'heater'

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Table 1 *Rates of emergency surgery and overall mortality in untreated patients with stigmata of recent haemorrhage*

	Type of SRH					
	Arterial bleeding		Non-arterial bleeding		Non-bleeding visible vessel	
Study	Emergency surgery	Mortality	Emergency surgery	Mortality	Emergency surgery	Mortality
Swain *et al.*[36]	2/4	2/4	—	—	12/24	5/24
Vallon *et al.*[35]	9/13	3/13	—	—	5/16	3/16
Papp[52]	—	—	—	—	7/16	1/16
Rutgeerts *et al.*[42]	—	—	5/40	6/40	6/26	4/26
Swain *et al.*[44,45]	6/9	2/9	—	—	11/29	5/29
Freitas *et al.*[56]	1/2	1/2	4/8	1/8	8/17	3/17
Panes *et al.*[76]	5/13	0/13	7/24	3/24	8/21	1/21
Chung *et al.*[78]	7/10	0/10	7/24	2/24	—	—
Total	30/51 (59%)	8/51 (16%)	23/96 (24%)	12/96 (12%)	57/149 (38%)	22/149 (15%)

SRH, stigmata of recent haemorrhage

probe. Injection therapy has focused mainly on ethanol, the sclerosant polidocanol and adrenaline, the last two being used alone or in combination. Before concentrating on these approaches, however, there are other, less well known techniques which require a brief mention.

Clotting factors in the form of cryoprecipitate or thrombin can be delivered endoscopically to bleeding lesions by spraying[22,23], injection[24,25] or ferromagnetic tamponade[26,27]. Similarly, topical application of microcrystalline collagen can be used to initiate clotting[28,29], and tissue adhesive in the form of trifluoroisopropyl cyanoacrylate has been given a trial[30]. Mechanical methods of endoscopic haemostasis have also been described, utilizing balloon tamponade of the duodenal bulb[31] and direct placement of clips on to exposed vessels[32]. These techniques have met with varying degrees of success, however, and have not been widely investigated or employed.

Laser photocoagulation

Details of the mechanism of laser photocoagulation are available elsewhere[5,33]. Suffice it to say that on contact with tissue, laser light is converted to heat which causes coagulation and vaporization. Two types of laser have been used in the treatment of bleeding ulcers – the argon ion and the neodymium yttrium aluminium garnet (Nd YAG). The former produces a blue-green light which is largely absorbed by haemoglobin so that tissue penetration is low, especially in the presence of blood. The Nd YAG laser on the other hand, has greater tissue penetration[34] and therefore has a theoretical advantage over the argon laser where active bleeding and large vessels are concerned.

In recent years, considerable clinical experience with laser photocoagulation has accumulated, and the most instructive way in which to assess its impact is to examine the 11 controlled trials which have been published. In a study of 136 patients with arterial bleeding, non-bleeding visible vessels or other stigmata of recent haemorrhage (SRH), Vallon and others could not demonstrate an overall significant reduction in the need for emergency surgery or mortality using the argon laser. However, if patients with ulcers inaccessible to laser treatment were excluded from the analysis, a significant improvement was seen in the group with arterial bleeding[35]. In apparent contrast, the study conducted by Swain and his colleagues showed a clear advantage for the argon laser in terms of emergency surgery and mortality in patients with arterial bleeding or visible vessels. However, of 108 patients eligible to enter this trial, 32 were excluded before randomization, largely because the lesion was not accessible to the laser beam[36]. The third argon laser trial was much smaller, but of seven treated patients with arterial bleeding or a visible vessel, none required surgery, compared with five out of nine similar controls[37].

Turning now to the Nd YAG laser, there have been eight trials to date, but four of these were poorly designed or failed to give adequate definitions of the bleeding lesions treated[38–41]. The remaining studies, however, were more carefully constructed and executed, and therefore deserve closer consideration. Rutgeerts and his colleagues randomized 129 patients with non-arterial bleeding, visible vessels or clot, and achieved 100 per cent initial haemostasis in the laser-treated group[42]. They observed no differences in mortality rate or the need for emergency surgery, but laser therapy did produce a significant reduction in clinical rebleeding among the patients with active bleeding. It should be noted that 20 subjects were excluded from this study because of equipment failure and eight because of inability to gain adequate access to the lesion. In a smaller trial from Glasgow, 20 patients with visible vessels were randomized, but of 12 allocated to laser therapy, only eight actually received treatment[43]. Emergency surgery was required in one of the treated patients compared with all eight of the controls, and this constituted a significant advantage for laser photocoagulation even when the untreated patients in the laser group were included.

The largest favourable study of the Nd YAG laser has been that of Swain and his co-workers[44]. This trial recruited 138 patients with arterial bleeding, visible vessels or other stigmata of recent haemorrhage and demonstrated a significant reduction in rebleeding rate, the need for surgery and mortality rate[44,45]. Unfortunately, a large number of eligible patients were excluded from this trial, mainly because of technical difficulty in aiming the laser beam. In the most recently reported trial, Krejs and others randomized 174 patients but did not find any significant benefit from the laser treatment[46]. Before entry into this study 281 potential subjects were excluded, 221 because they were too unstable to be moved to the laser unit, 26 because the laser was not functioning and 34 because the lesion was inaccessible. It is also important to note that only two of the trial patients had active arterial bleeding, and that laser treatment was carried out by, or under the supervision of, five different operators. The poor results of this trial may therefore have been influenced by a tendency to select low-risk patients and to have treatment delivered by multiple operators of variable experience.

In summary, there have been eleven controlled trials of laser therapy for non-variceal upper gastrointestinal haemorrhage, but not all are of similar quality. In six of these reports a significant benefit has been claimed[36,37,41–44], but in fact only four trials have shown a reduction in the need for emergency surgery[36,37,43,44] and only two have demonstrated a significant reduction in mortality rate[36,44]. Furthermore, these benefits must be set against the relatively large number of patients excluded from randomization in at least three of the studies[36,42,44]. There is little doubt, however, that laser photocoagulation can be effective in producing permanent haemostasis, but it is highly operator-dependent, and can only be used for lesions which are favourably situated within the gastrointestinal tract.

Electrocoagulation

Electrocoagulation is an extremely useful haemostatic technique in surgery and can be applied to endoscopic haemostasis. Monopolar electrodes are effective in this respect, but carry the disadvantages of unpredictable depth of thermal injury, adherence to tissue and clot dislodgement[5]. These may be overcome by irrigating the tip of the probe so that it is covered by a film of water (the liquid monopolar electrode)[47] or by employing the bipolar principle. As a conventional bipolar electrode would be difficult to position endoscopically, a multipolar probe (BICAP®, ACMI, Stamford, Connecticut, USA) has been developed, the tip of which carries three equally spaced pairs of bipolar microelectrodes[48].

Despite the problems associated with 'dry' monopolar electrodes they have been reasonably successful in controlling non-variceal bleeding, and four uncontrolled studies have produced impressive rates of initial and permanent haemostasis in actively bleeding lesions using this approach[49-52]. There have been two controlled trials, and in the first Papp reported a significant reduction in rebleeding and need for surgery in patients with non-bleeding visible vessels[52]. In the second trial 37 patients with gastric ulcers exhibiting visible vessels were randomized, and a significant reduction in rebleeding was achieved by therapy, especially among those with active bleeding[53]. Although no complications were reported in these studies, it is important to heed the early experience of Koch and others who produced three perforations with one death after the successful control of bleeding in 15 patients[54]. Clearly, the dry monopolar electrode can be dangerous and must be used with extreme skill and care. There has been less clinical experience with the liquid monopolar electrode, but in one study permanent haemostasis was achieved in 11 out of 15 patients with actively bleeding lesions[55], and in a randomized trial a significant reduction in rebleeding and the number of emergency operations was produced in those patients with non-bleeding visible vessels[56].

The multipolar electrode has received more attention, but although early experience indicated that it could be useful[57,58], two controlled trials have shown no benefit[59,60] and a third, although demonstrating a significant reduction in rebleeding, did not show a reduction in the need for emergency surgery or mortality rate[61]. One investigator, however, has achieved much better results. In a randomized study of 44 patients with actively bleeding lesions, Laine demonstrated significant reductions in emergency surgery, amount of blood transfused, duration of hospital stay and overall cost of treatment[62]. Further, in a separate trial involving 74 patients with non-bleeding visible vessels similar results were reported by the same author[63]. It is important to note that Laine used a 10 Fr probe, as opposed to the small 7 Fr electrode employed by the other workers. This may go part of the way towards explaining the difference in results, although operator skill may have been a crucial factor, as no patient had to be excluded from Laine's series owing to profuse bleeding or poor access.

Direct thermal coagulation

Direct thermal coagulation can be produced by means of a heater probe consisting of an aluminium tip coated by non-stick TEFLON® (Du Pont de Nemour Incorporated, UK) which is heated to 250°C by an inner coil[64]. There is relatively little published clinical experience of the heater probe, but three non-randomized studies testify to its ability to produce initial and, in some cases, permanent haemostasis in bleeding peptic ulcers[65-67]. In two of these reports, particular difficulty was encountered in controlling bleeding from duodenal ulcers[66,67], but this was not the experience of Johnston and others who achieved 100 per cent initial haemostasis in 20 patients, 11 of whom had duodenal ulcers[65].

To date, only one controlled trial of the heater probe has been reported. In this study 43 patients with active bleeding or major SRH were randomized and a significant reduction in rebleeding was demonstrated in the treated group[68]. There was, however, no difference in terms of surgery or mortality rates and there were eight exclusions from the trial for technical reasons[69].

Injection therapy

Injection treatment for non-variceal bleeding has only commanded attention relatively recently. The substances which have been used fall into two categories – sclerosants and vasoconstrictors used alone or in combination. The main sclerosant materials in current use are ethanol and polidocanol, both of which act by thrombosing the bleeding vessel and causing necrosis with subsequent fibrosis of the surrounding tissue[1]. Adrenaline is the only vasoconstrictor which has been formally evaluated, and is presumed to operate via temporary vasoconstriction and platelet aggregation which combine to encourage thrombosis in the bleeding vessel[70].

Using 98 per cent ethanol, Asaki and his colleagues have accumulated the largest series of patients treated by injection therapy. In a multicentre study involving 332 patients with active bleeding or adherent clot, only two continued to bleed, 20 rebled and 10 required emergency surgery[71]. In a much smaller study, Sugawa and others achieved permanent haemostasis in 34 out of 40 patients with actively bleeding lesions using the same method[72]. Polidocanol has also emerged as a clinically useful sclerosant and three uncontrolled studies, one using the substance alone[73] and two employing pre-injection with adrenaline[74,75], have demonstrated its efficacy in both actively bleeding and non-bleeding vessels. To date, there has been one controlled trial of polidocanol in which 113 patients with ulcers exhibiting active bleeding, visible vessels or adherent clot were randomized. The treated group received an initial injection of 1:10000 adrenaline into and around the bleeding point, followed by 1 per cent polidocanol administered in the same way. Overall, there were significant reductions in the need for emergency surgery, amount of blood transfused and duration of hospital stay[76]. Six patients were excluded from this study because their ulcers were inaccessible owing to duodenal deformity.

The use of adrenaline as the sole injectable agent has received scanty attention until recently, but there is now evidence that it may be of value. After an encouraging pilot study[77], a group from Hong Kong has reported on a randomized trial of 1:10000 adrenaline injection which involved 68 patients with actively bleeding ulcers[78]. Strict criteria for selecting patients for emergency surgery were employed, and adrenaline injection was found to produce a significant decrease in the need for such treatment, as well as reductions in the amount of blood transfused and time in hospital. Hirao and co-workers have also reported success with adrenaline, although their technique also involved the injection of hypertonic saline[79]. In this context it is of interest that two groups have produced a marked improvement in the efficacy of Nd YAG laser therapy by prior injection of adrenaline[80,81]. This has been ascribed to good visualization of the bleeding point and elimination of the arterial heat sink[82], but it is equally possible that the vasoconstrictor exerted the major therapeutic effect. The same argument can be applied to combinations of adrenaline and sclerosant.

Comparisons between different methods

There have been relatively few studies comparing different techniques of endoscopic haemostasis. Goff looked at Nd YAG laser therapy and multipolar electrocoagulation in 33 patients with active bleeding or visible vessels[83] and could find no difference. This was a small group, however, and only partly randomized. In a larger, better designed prospective trial, Rutgeerts and others similarly compared the Nd YAG laser with the multipolar electrode and found them to be equally effective[82]. In this study, however, both forms of coagulation were preceded by adrenaline injection, making interpretation of the results difficult.

The Nd YAG laser has also been compared with the heater probe, and in a non-randomized retrospective study Johnston came down in favour of the heater probe. Emergency surgery was required in only 5 per cent of 20 subjects treated by the probe, whereas 17 per cent of the 35 laser-treated patients came to operation[65]. In a three-way randomized trial, however, Northfield and his colleagues have reported significantly less rebleeding with Nd YAG laser treatment when compared with controls, but not with heater probe therapy[84].

Finally, in another three-pronged trial comparing multipolar electrocoagulation, heater probe and non-treated controls, Jensen and others found that both forms of therapy were effective in obtaining initial haemostasis, but that only the heater probe produced a significant reduction in rebleeding and the need for urgent surgery[85].

Although randomized trials may be seen as the ideal way of establishing the best form of endoscopic haemostasis it must be accepted that any investigator will obtain optimum results from the type of therapy with which he or she is most familiar. Until trials that overcome this obstacle are carried out, it will remain necessary to draw conclusions from separate studies. This can be awkward, as stratification of patients into various levels of risk is not always possible from the data in the available literature, but a certain amount of comparative analysis is possible. As outlined in the introduction, only patients with active bleeding at the time of endoscopy or visible vessels are at real risk of requiring emergency surgery or of dying from bleeding. In addition, as can be seen from *Table 1*, those with arterial bleeding are at greater risk than those with simple oozing haemorrhage. It is only instructive, therefore, to compare different studies within appropriate subgroups, and an attempt has been made to do this using three broad categories: laser photocoagulation, electrocoagulation and injection techniques (*Table 2*). Unfortunately, many published reports simply do not contain sufficiently detailed information and cannot therefore be used for comparison. In addition, the groups are clearly heterogeneous and the electrocoagulation results are heavily biased by one study. With these provisos, however, it would seem that while all three methods are roughly equivalent in the treatment of non-arterial bleeding and visible vessels, laser therapy of arterial bleeding is not as effective as electrocoagulation or injection.

Discussion

The current profusion of techniques for endoscopic haemostasis indicates that no one method has gained supremacy. Laser photocoagulation has been in the forefront for a number of years, but careful appraisal of the literature does not inspire great confidence in this approach. Few of the controlled trials have demonstrated clear benefit from laser treatment, and the overall results for arterial bleeding are not impressive. Furthermore, in several trials relatively large numbers of patients had to be excluded because their lesions were inaccessible[36,42,44,46,82], a problem which is less common with other forms of therapy. Equipment malfunction, absence of the laser operator and inability to transfer patients to the laser facility are also frequently cited reasons for treatment failure[36,42-46] and adverse effects including perforation and reactivation of bleeding have been reported[36,46,65,80]. Finally, laser equipment is expensive and its widespread introduction for endoscopic haemostasis cannot yet be justified.

What then, of the alternatives? Electrocoagulation offers a simpler approach, and despite its theoretical disadvantages the monopolar electrode does appear to be useful, although it still requires careful prospective evaluation. Evidence from randomized trials indicates that the 10 Fr multipolar electrode is more likely to be effective than the 7 Fr probe, but it should be stressed that only one investigator has been able to demonstrate a significant reduction in the need for emergency surgery using this device[62,63]. The heater probe is also an attractive concept and shows some promise at an early stage of its clinical development. All these coagulation instruments do carry a risk of extensive tissue damage and perforation, but in practice this does not seem to be a major problem. They also involve extra cost, although not of the same order as laser units.

The final approach is injection therapy which has the attraction of demanding little extra equipment beyond an upper gastrointestinal endoscope. It is not clear, however, which of the injectable agents is most satisfactory. Spectacular results have been obtained from Japan using ethanol[71], but there has been little confirmatory evidence as yet. The sclerosant polidocanol also seems effective, but most of the studies, including the only controlled trial, also utilized preinjection with adrenaline[74-76]. Adrenaline alone would seem to be effective in actively bleeding lesions[77,78] and does not carry the risk of ulcer extension and perforation occasionally seen with sclerosants[71,73]. Having said this, further controlled studies are needed to define the value of adrenaline more precisely, and although no adverse systemic effects have been reported, care must be exercised in its use.

Whatever method is employed it is important to be able to predict which patients will benefit from endoscopic haemostasis and in which it will be unnecessary or fail. Appraisal of the data from randomized trials would indicate that all patients with active bleeding or visible vessels should be seriously considered for therapy at the time of endoscopy, whereas those with minor stigmata of recent haemorrhage or clean ulcers are unlikely to require active treatment. The question of which lesions will not respond permanently to endoscopic intervention is still unresolved, and represents a crucial area for future research. At present the only obvious contraindication is inability to apply the chosen therapeutic modality because of access difficulty or torrential bleeding.

Before concluding this review some technical points should be emphasized. Primarily, it must be understood that even diagnostic endoscopy requires considerable skill in the presence of bleeding, and haemostasis should not be attempted by an inexperienced operator. The endoscopist must also be prepared to carry out gastric lavage, preferably with the aid of an overtube for airway protection[86], and to use vigorous washing in order to obtain a good view[87]. Likewise, the importance of routine repeat endoscopy within 24 h of successful initial haemostasis cannot be overstated, as this affords a valuable opportunity for further therapy should subclinical rebleeding have occurred[78,82].

Endoscopic treatment for non-variceal bleeding is in a state of flux, and the way forward must be to establish the optimum technique or combination of techniques. In a recent leading article, Schuman suggested setting up a multicentre trial to establish whether 'injection therapy can become the frontline endoscopic management for upper gastrointestinal bleeding or whether it is just too good to be true'[88]. Pre-empting this proposal, Rutgeerts has initiated a trial comparing adrenaline alone, adrenaline followed by polidocanol and adrenaline followed by laser therapy[89]. The final result of this study will be of great interest and it may be that other combinations will prove to be of value[90]. In the meantime we may be confident that endoscopic haemostasis will soon become recognized as the initial treatment of choice in most cases of upper gastrointestinal haemorrhage where intervention is indicated. With the present availability of simple and relatively inexpensive methods, it should be feasible to offer this service wherever standard equipment and a reasonable level of expertise exist, and conventional surgery for bleeding may become a rarity in the near future. It therefore behoves all surgical gastroenterologists to work in very close collaboration with their endoscopically trained colleagues or to be endoscopists themselves.

Table 2 *Rates of emergency surgery and overall mortality rate for different forms of endoscopic haemostasis. Omission of figures indicates that the subgroup was not studied or that the data were inadequate*

	Arterial bleeding		Non-arterial bleeding		Non-bleeding visible vessel	
Study	Emergency surgery	Mortality	Emergency surgery	Mortality	Emergency surgery	Mortality
Laser:						
Laurence *et al.*[91] (argon)	12/36	4/36	1/24	1/24	—	—
Vallon *et al.*[35] (argon)	7/15	2/15	—	—	6/19	3/19
Swain *et al.*[36] (argon)	4/7	0/7	—	—	4/17	0/17
Rutgeerts *et al.*[42] (Nd YAG)	14/23	7/23	1/46	6/46	2/17	2/17
Swain *et al.*[44,45] (Nd YAG)	2/10	1/10	—	—	2/25	0/25
Heldwein *et al.*[81] (Nd YAG)	19/30	11/30	—	—	9/21	4/21
Rutgeerts *et al.*[80] (adrenaline + Nd YAG)	4/26	4/26	—	—	3/28	1/28
Rutgeerts *et al.*[82] (adrenaline + Nd YAG)	5/12	—	0/9	—	1/29	—
Heldwein *et al.*[81] (adrenaline + Nd YAG)	3/6	2/6	—	—	4/26	0/26
Total	70/165 (42%)	31/153 (20%)	2/79 (2%)	7/70 (10%)	31/182 (17%)	10/153 (6%)
Electrocoagulation:						
Papp[52] (monopolar)	13/86	9/86	—	—	1/16	0/16
Freitas *et al.*[56] (monopolar)	3/4	1/4	1/7	0/7	2/14	1/14
Moreto *et al.*[53] (monopolar)	0/6	1/6	1/10	0/10	—	—
Rutgeerts *et al.*[82] (adrenaline + multipolar)	3/15	—	1/6	—	3/29	—
Laine[63] (multipolar)	—	—	—	—	3/37	1/37
Total	19/111 (17%)	11/96 (11%)	3/23 (13%)	0/17	9/96 (9%)	2/67 (3%)
Injection:						
Soehendra *et al.*[74] (adrenaline + polidocanol)	0/22	0/22	1/27	0/27	0/8	1/8
Sugawa *et al.*[72] (ethanol)	4/10	—	2/27	—	0/6	—
Panes *et al.*[76] (adrenaline + polidocanol)	1/15	0/15	0/22	1/22	2/18	1/18
Kortan *et al.*[75] (adrenaline + polidocanol)	4/32	—	0/24	—	—	—
Leung and Chung[77] (adrenaline)	1/12	—	2/25	—	—	—
Chung *et al.*[78] (adrenaline)	3/9	0/9	2/25	3/25	—	—
Steele *et al.*[92]* (adrenaline)	2/15	1/15	—	—	—	—
Total	15/115 (13%)	1/61 (2%)	7/150 (5%)	4/74 (5%)	2/32 (6%)	2/26 (8%)

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Repeat selective visceral angiography in patients with gastrointestinal bleeding of obscure origin

W. Y. Lau, H. Ngan*, K. W. Chu and W. K. Yuen

*Surgical 'C' Unit, Queen Elizabeth Hospital, Hong Kong, and *Department of Diagnostic Radiology, University of Hong Kong, Hong Kong*

Correspondence to:
Dr W. Y. Lau, Surgical 'C' Unit, Queen Elizabeth Hospital, Wylie Road, Hong Kong

In the past 9 years, we have operated on 56 patients with gastrointestinal bleeding of obscure origin. Selective visceral angiography demonstrated the bleeding lesions in 24 of the 30 patients who underwent this investigation. Six of these 24 patients, however, had a negative angiogram initially and the lesions were only demonstrated on a repeat angiogram. The negative initial angiograms were due to: (1) slow bleeding from lesions in two patients; (2) a small bleeding tumour that caused only intermittent jejunojejunal intussusception in one patient; (3) technical fault in one patient; and (4) spasm of the bleeding vascular lesions and their feeding arteries in two patients. We advocate repeat angiography the following day in all patients in whom profuse bleeding continues, and during the next intestinal bleeding in those whose bleeding stops after the initial negative angiography. In patients who have repeated episodes of massive bleeding, and in whom full investigations fail to reveal the bleeding source, repeat angiography carried out 4 weeks after the bleeding has stopped can sometimes demonstrate the vascular lesions.

Keywords: Gastrointestinal bleeding, selective visceral angiography, bleeding lesions

Gastrointestinal bleeding is a common emergency. Fortunately, most of the bleeding lesions are situated at sites easily accessible to endoscopic examination and diagnosis can be speedily made in 80–90 per cent of patients by emergency oesophagogastroduodenoscopy alone[1,2]. In the minority of patients who remain undiagnosed after conventional investigations, many will never bleed again[3,4]. A problem, however, arises when bleeding becomes massive, continuous or recurrent. The investigation of such patients is notoriously difficult, and very often demands a disproportionately large amount of medical time and resources[3].

Selective visceral angiography has proved to be valuable in the diagnosis and localization of these bleeding lesions[4]. The angiogram will be positive in lesions with bleeding rates $>0{\cdot}5$ ml/min (Reference 5) and occasionally in lesions from which the bleeding has stopped[6]. The place of repeat angiography in a patient who has previously had a negative angiography is less well defined. Many clinicians doubt whether repeat angiography will give additional information. Most of them are reluctant to press for repeat angiography and they feel embarrassed when the angiography turns out to be negative again. Thus, information is needed about the value of repeat angiography. In the past 9 years, we have found repeat angiography to be useful and our experience forms the basis of this report.

Patients and methods

From 1979 to 1988, we operated on 56 patients who presented with gastrointestinal bleeding of obscure origin. These patients are defined as patients in whom we failed to find the bleeding source after conventional investigations. The investigations included at least one emergency upper gastrointestinal endoscopy, barium meal, barium enema, sigmoidoscopy and colonoscopy[4]. All patients had massive, continuous or recurrent bleeding. They represented 1·5 per cent of all patients admitted to our unit for gastrointestinal bleeding during the period of study.

A careful history, including a family history of gastrointestinal bleeding and a history of drug intake, was routinely taken. The facial stigmata of Peutz–Jeghers syndrome, blue rubber-bleb naevus syndrome[7] and skin telangiectasia of hereditary haemorrhagic telangiectasia[6] were especially sought in the physical examination. Blood dyscrasias, clotting defects and other metabolic disorders were excluded by laboratory investigations. When conventional investigations failed to reveal the bleeding source, the patients were investigated with ^{99m}Tc-labelled pertechnetate scan, contrast study of the small intestine, selective visceral angiography and ^{99m}Tc-labelled red blood cell scan in the manner we have reported previously[4]. Emergency angiography was carried out whenever the bleeding rate was thought to be $>0{\cdot}5$ ml/min. As far as possible, we tried to localize the lesions before surgical treatment. During the period of investigation, these patients were monitored closely and they were managed actively with blood transfusions.

We repeated the selective visceral angiography the following day in patients in whom profuse bleeding continued, and during the next intestinal bleed in those patients whose bleeding stopped after the initial negative angiography. In patients who had repeated episodes of massive bleeding and in whom full investigations failed to reveal the bleeding source, we carried out repeat angiography 4 weeks after the bleeding had stopped.

Results

Of the 56 patients on whom we operated for occult bleeding lesions, 30 patients underwent selective angiography. Of these 30 patients 24 had the lesions localized by angiography (80 per cent). Six of these 24 patients (25 per cent), however, had a negative angiogram initially. The lesions were subsequently demonstrated on repeat selective angiography (*Table 1*).

The causes of failure of the initial angiography in our patients were as follows (*Table 2*):

1. Slow bleeding from the lesion in two patients.
2. A small bleeding tumour that caused intermittent jejunojejunal intussusception in one patient. The repeat angiography was carried out during the intussusception (*Figure 1a* and *b*).
3. Technical fault in one patient (this occurred in a very obese patient who had a small intestinal arteriovenous malformation). On the first angiogram, the arteriovenous malformation was outside the edge of the radiography and it was missed. On repeat angiography, the lesion was detected in the left lower abdomen.
4. Spasm of the bleeding vascular lesions and their feeding arteries in two patients. The vascular lesions that were detected on repeat angiography were completely absent in the initial angiogram carried out at the time of bleeding. The proximal

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Table 1 *Selective angiography and repeat angiography in the localization of occult bleeding lesions*

Pathology	Number of patients	Number of patients with lesions: Localized by initial angiography	Localized by repeat angiography
Tumours			
Lymphoma of small intestine	9	2	—
Smooth muscle tumours of small intestine	8	2	1
Ileal angiosarcoma	1	—	—
Jejunal carcinoma	1	—	—
Chronic myeloid leukaemia with ileal leukaemic ulcer	1	1	—
Vascular			
AVM of the stomach	1	1	—
AVM of the small intestine	6	3	3
AVM of the rectum	2	2	—
Angiodysplasia of caecum	7	6	1
Polyarteritis nodosa	1	1	—
Diverticula			
Meckel's diverticula	11	1	—
Jejunal diverticula	2	1	—
Benign ulcers			
Non-specific ileal ulcers	2	1	1
Steroid-induced jejunal ulcer	1	1	—
Tuberculous ileal ulcers	1	1	—
Others			
Leaking aortoduodenal fistula	1	—	—
Ischaemic colitis	1	1	—
Total	56	24	6

AVM, arteriovenous malformation

Table 2 *Use of repeat angiography in patients with gastrointestinal bleeding of obscure origin*

Patient	Site of lesion	Pathology	Clinical presentation	Time interval between two angiographies	Indications for repeat angiography	Findings of repeat angiography
1	Jejunum	AVM	Intermittent bleeding	3 months	Recurrent active bleeding	Contrast extravasation into gut lumen
2	Ileum	Non-specific ulcer	Massive bleeding	1 day	Continuous active bleeding	Contrast extravasation into gut lumen
3	Jejunum	Smooth-muscle tumour	Intermittent bleeding, intestinal colic	2 years	Recurrent bleeding	Jejunojejunal intussusception
4	Jejunum	AVM	Slow continuous bleeding	2 days	Continuous bleeding	AVM of small intestine. Failure of first angiogram due to technical fault
5	Jejunum	AVM	Recurrent massive bleeding	4 weeks	Suspected intestinal vascular lesion	AVM of small intestine. Lesion and distal portion of feeding artery not seen in first angiogram
6	Caecum	Angiodysplasia	Recurrent massive bleeding	4 weeks	Suspected intestinal vascular lesion	Caecal angiodysplasia. Lesion and its feeding artery not seen in first angiogram

AVM, arteriovenous malformation

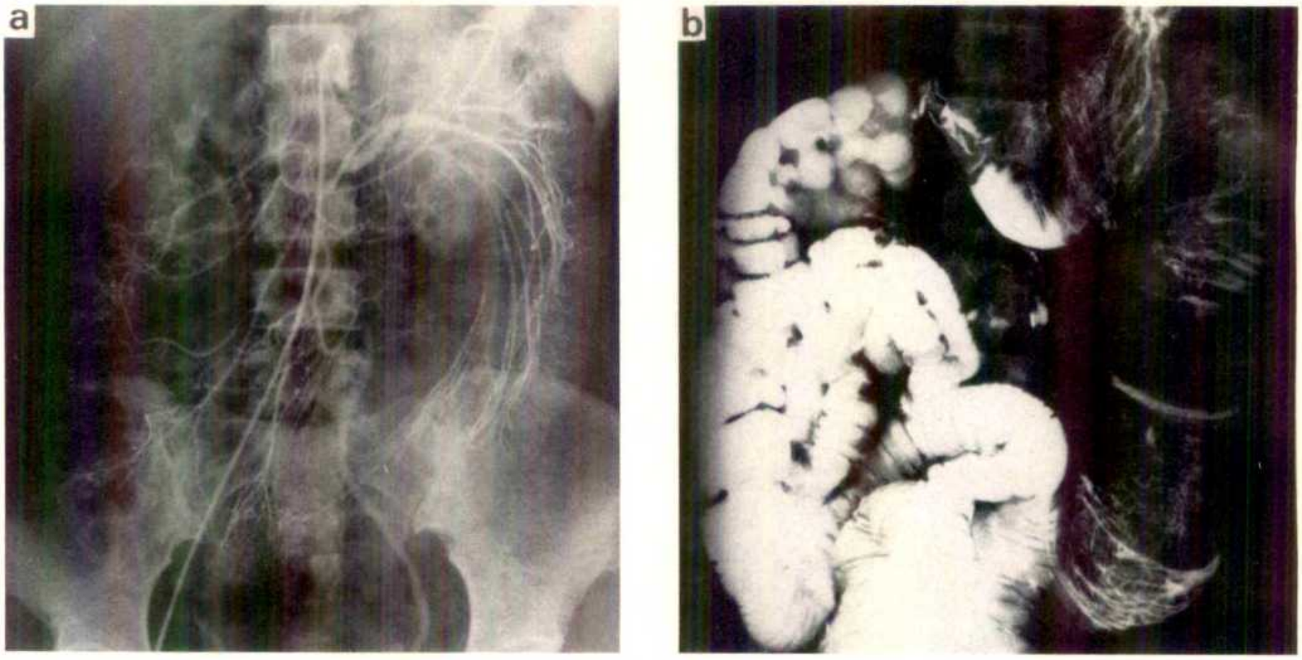

Figure 1 **a** *Late arterial phase of superior mesenteric angiogram, showing a grossly dilated loop of proximal jejunum in the left side of the abdomen.* **b** *Subsequent barium meal and follow-through examination, showing jejunojejunal intussusception in the left side of the abdomen*

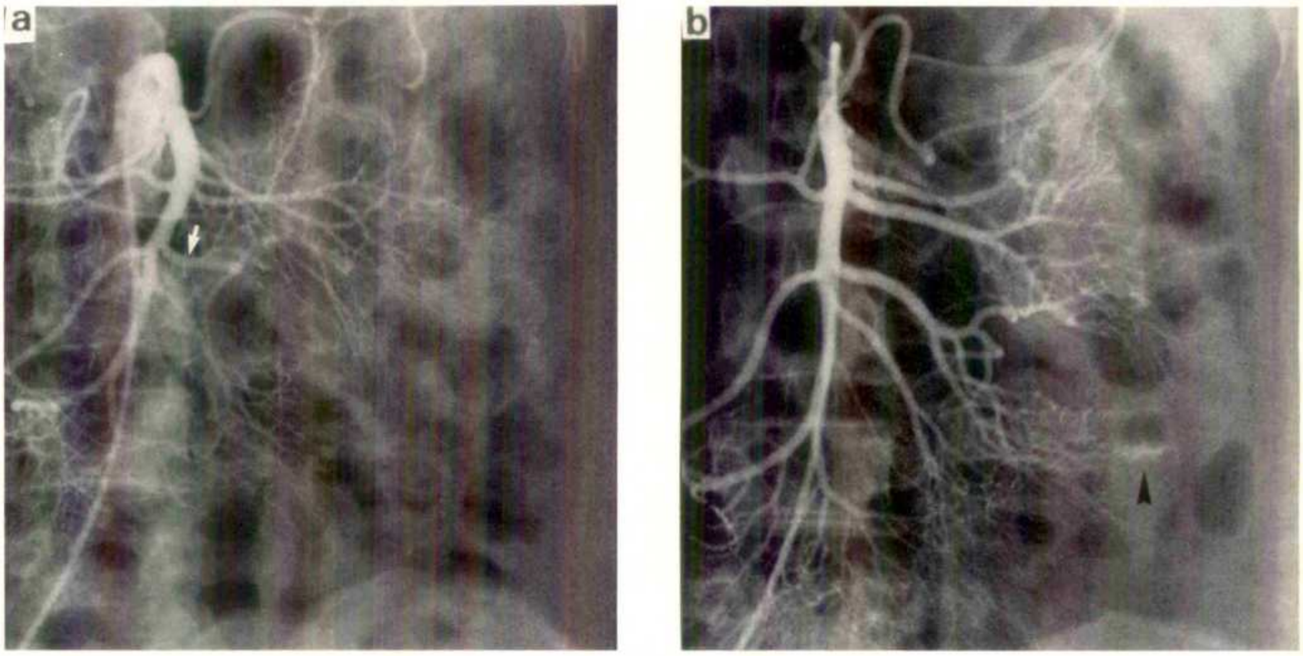

Figure 2 **a** *Initial angiography carried out at the time of bleeding, showing the absence of the small intestinal arteriovenous malformation with attenuation of the proximal portion and complete disappearance of the distal portion of the feeding artery (white arrow).* **b** *Repeat angiography 4 weeks later, showing a small intestinal arteriovenous malformation (arrowhead) and a normal feeding artery*

portion of the feeding artery was attenuated and the distal portion disappeared as a result of spasm in the initial angiogram in one patient (*Figure 2a* and *b*). In another patient, the entire feeding artery disappeared.

Discussion

Selective visceral angiography is important in the management of patients with recurrent gastrointestinal bleeding of obscure origin[4-6,8-10]. Almost all these patients have already had repeated upper and lower gastrointestinal endoscopies, barium meal and barium enema examinations without locating the bleeding lesions[4]. When small-bowel contrast examinations are also negative, approximately 25 per cent of these patients will have intestinal vascular lesions demonstrated on selective angiography. Approximately 20 per cent of the remainder will have other angiographically identifiable lesions, such as leiomyoma, mesenteric artery aneurysm or Meckel's diverticulum[8,11]. Extravasation of contrast into the gut lumen will be demonstrated angiographically for lesions with bleeding rates >0·5 ml/min (Reference 5). The presence of a lesion with a potential to bleed does not mean it is the source of bleeding, unless it is observed directly, endoscopically or radiologically to be actively bleeding[9,10]. This is important because angiodysplasia of the right colon has been found in one-quarter of people over the age of 60 years, without any evidence of bleeding[10,12].

Angiography is also valuable in distinguishing between solitary and multiple lesions[6]. In the latter instance, the location and extent of each lesion are the prime determinants of resectability[6,7]. Furthermore, for patients with a positive angiography, a superselectively prepositioned angiographic catheter will allow intra-operative localization of the segment of gut containing the bleeding lesion[4,13,14].

The importance of repeating the selective angiography has been observed by other workers[15,16] Miller *et al.* commented that, for unknown reasons, intestinal vascular lesions might not be apparent on one examination and yet be obvious on another[15]. Similarly, Marx *et al.* also reported that the reasons for failure of the initial angiography were not always evident. They postulated that the possible causes of failure might be faulty radiological techniques (which was the cause of failure in patient 4) and the small size of the lesions, which might escape careful scrutiny by the radiologist[16] (as in the case of patient 1). Crawford and Russell first used the term 'cryptic' intracranial vascular malformation to denote a small lesion that is not detected by angiography but is identified by pathological examination as a cause of spontaneous intracranial haemorrhage[17]. Patient 1 of our study probably had an intestinal counterpart of this lesion. In patients 1 and 2, extravasation of the contrast medium was not visible in the initial angiograms, probably because the rate of bleeding was slower during the procedure than during the repeat angiograms.

The fact that vascular lesions and the distal portions of their feeding arteries may not be visualized in the initial angiography but are evident on repeat angiography (as in patients 5 and 6) suggests the probability of spasm of these abnormal vascular channels and their feeding arteries. This may be a physiological response to bleeding, so that blood may not pass through the channels during angiography[16]. Transient spasm of intracranial arteriovenous malformations and their feeding vessels after haemorrhage has been reported[18], and there is no reason why this cannot occur in intestinal vascular lesions. Indeed, this haemodynamic change has been postulated to be one of the possible causes of failure of the initial angiography in patients with intestinal arteriovenous malformation[16] and we were able to demonstrate its existence in patients 5 and 6.

In patient 3, we were fortunate to have repeated the angiography during an attack of intussusception. Otherwise, the small smooth muscle tumour forming the head of the intussusceptum would have been too small to be demonstrated by angiography.

From our experience, we advocate that angiography should be repeated on the following day in all patients in whom profuse bleeding continues, and during the next attack of intestinal bleeding in those whose bleeding has stopped after the initial negative angiogram For patients who have repeated episodes of massive bleeding, and in whom full investigations including angiography during an attack of bleeding fail to reveal the bleeding source, repeat angiography carried out 4 weeks after the bleeding has stopped can sometimes demonstrate the vascular lesion.

Acknowledgements

We thank Dr Corinna Har, Mrs Stella Rumjahn and Mrs Irene Wong for their help in the preparation of this paper.

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Changing pattern of admissions and operations for duodenal ulcer

K. D. Bardhan, G. Cust*, R. F. C. Hinchliffe, F. M. Williamson*, C. Lyon* and K. Bose

*District General Hospital, Rotherham and *Trent Regional Health Authority, Sheffield, UK*

Correspondence to:
Dr K D. Bardhan, District General Hospital, Moorgate Road,
Rotherham S60 2UD, UK

The admission rates for duodenal ulcer (DU) and the effect of H_2-receptor antagonists (H_2RA), introduced in the Trent Region of the UK in 1977, were examined. The admission rates are expressed per 10^6 of resident population. The use of H_2RA has risen 3·7-fold (from 1978 to 1983), yet overall admission rates for perforation have changed little: 99 in 1972–76 (pre-H_2RA period) compared with 103 in 1977–84 (H_2RA period). Admission rates for haemorrhage have risen by 8 per cent, from 130 to 140 ($P < 0{\cdot}01$). However, the overall rates conceal large increases ($P < 0{\cdot}01$) in the admission rates for those aged ≥65 years, of 33 per cent (from 264 to 352) for perforation and of 28 per cent (from 381 to 489) for haemorrhage. Emergency admissions for uncomplicated DU were unchanged: 88 in 1972–76 and 89 in 1977–84. However, the proportions operated on fell by 58 per cent ($P < 0{\cdot}01$), from 30 per cent of admissions in the pre-H_2RA period compared with only 12 per cent in the H_2RA period. Waiting-list admissions for uncomplicated DU fell by 43 per cent, from 187 to 106 ($P < 0{\cdot}01$), and the proportions operated on fell from 162 to 76; the combined effect resulted in a reduction of 53 per cent in the operation rates ($P < 0{\cdot}01$). In Rotherham, the use of H_2RA has risen 6·2-fold (from 1978 to 1983) and they were generally used intermittently in 1976–78 and later for maintenance therapy and high-dose treatment. Yet admissions for perforation and for haemorrhage were unchanged. Emergency admissions for uncomplicated DU rose by 40 per cent, from 130 in 1972–75 to 182 in 1976–84, but the proportions operated on fell markedly, from 20 to 6 per cent ($P < 0{\cdot}01$); waiting-list admissions fell in 1976–78 by 29 per cent and in 1979–84 by 73 per cent. The proportions operated on in the three periods fell from 74 to 53 per cent and 25 per cent respectively and these two factors led to decreases in elective surgery of 50 per cent in 1976–78 and 91 per cent in 1979–84 ($P < 0{\cdot}01$). Thus, H_2RA have not reduced emergency admissions in DU patients but they are associated with a reduction in waiting-list admissions and in the numbers operated on for uncomplicated DU; where the drugs have been used more intensively, the decrease has been even more marked. Much of this decline can be attributed to the changing natural history of the disease; however, when used intensively, H_2RA have a significant additional effect.

Keywords: Duodenal ulcer, elective surgery, perforation, haemorrhage, effect of age, histamine H_2 receptor antagonists

Hospital admissions for patients with duodenal ulcer (DU), both with and without complications, have been steadily declining in the UK since at least 1957[1–3] and in the USA since 1964[4–14]. The causes for this reduction remain unknown. Since 1977, when the histamine H_2-receptor antagonist (H_2RA) cimetidine became widely available, several centres in the UK, Europe and in the USA have reported further reductions in admission rates which have been attributed to the effectiveness of the drug in medical treatment[15,16]. However, the degree of reduction in admission rates of patients with uncomplicated DU or of patients with complications, and the proportions requiring elective surgery, have varied considerably in different parts of the world. It is not known whether this has any relation to the intensity with which cimetidine and more recently ranitidine have been used[17]

This study investigates the effect that the rising use of H_2RA in the Trent Regional Health Authority (RHA) has had on the admission rates of patients with DU, with or without complications, and on the need for elective surgery In addition a similar analysis was carried out among patients with DU admitted in Rotherham (in the county of South Yorkshire, which is in the Trent RHA) where there is a special interest in ulcer disease and where the H_2RA were used earlier and more extensively, to see if this had any greater influence on the admission and operation rates.

Patients and methods

Information concerning admissions of patients with DU was obtained from the Trent RHA Hospital Activity Analysis files, from which we created a special file concerning DU patients. This dealt with the numbers of patients admitted in each year from 1972 to 1984, subdivided by sex, and for age groups under 35 years, 35–64 years and 65 years or more. The data are presented as admission (age- and sex-specific where subdivided as indicated above) or operation rates per 10^6 of resident population (rounded to the nearest whole number). The current resident population in the Trent RHA is $4{\cdot}6 \times 10^6$

The following categories of DU patients admitted were examined (*Table 1*) (1) perforation, including perforation plus haemorrhage, (2)

Some of the data (up to 1983) were presented on a poster at the meeting of the British Society of Gastroenterology, Brighton, UK in March 1985.

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Table 1 *Categories of duodenal ulcer patients studied*

Category	8th edition ICD rubrics	9th edition ICD rubrics
Perforation, including perforation plus haemorrhage	532·00 532·01 532·02 532·03	532·1 532·2 532·5 532·6
Haemorrhage	532·91 532·92 532·93	532·0 532·4
Uncomplicated ulcer	532·90	532·3 532·7 532·9

ICD, International Classification of Disease, published by the World Health Organization. The 8th edition covers the period until the end of 1978 and the 9th edition from 1979 onwards. The 8th edition ICD provided only limited subdivisions of duodenal ulcer. To permit detailed analysis, a fifth digit was added by the Trent Regional Health Authority. However, the 9th edition ICD is more detailed than the 8th edition and divides duodenal ulcer into more subcategories. Each of the latter is therefore represented by four digits only

Table 2 *Operations that were searched in the Office of Population Censuses and Surveys coding to define all patients with uncomplicated duodenal ulcer*

Operation	OPCS code number
Partial gastrectomy	423·9
With gastroduodenostomy	423·2
With gastrojejunostomy	423·3
Vagotomy	
With gastroenterostomy	435
With pyloroplasty	436
Other types of vagotomy (includes truncal, selective and highly selective, i.e. proximal gastric, vagotomy)	434

OPCS, Office of Population Censuses and Surveys

haemorrhage, and (3) uncomplicated ulcer, subdivided according to admission (a) as an emergency (presumably for pain and/or vomiting) or (b) from the waiting list or as a 'booked' case

The Hospital Morbidity Record (HMR-1) form, from which the Hospital Activity Analysis files are created, allows up to six diagnoses to be recorded for each patient; these diagnoses are coded in order of importance for that particular admission. As we were interested in the incidence of admissions for perforation and for haemorrhage, all patients with either of these two diagnoses were included, irrespective of the coded position. In contrast, in patients with uncomplicated DU operation rates were of interest. To ensure the selection of patients who were admitted primarily because of their DU and not for another unconnected diagnosis or operation in which the DU was recorded routinely in a low diagnostic position, only those patients with DU listed in the first diagnostic position were counted. The numbers of these DU patients without complications who had any of the antiulcer operations listed in *Table 2* were also recorded. However, only the total number of patients operated on is presented.

By classifying the DU patients into three broad categories and by combining the antiulcer operations into one category, and after comparing the routine Hospital Activity Analysis data collected in Rotherham with samples of the individual case notes, we believe that errors in the routine analysis system are negligible. There have been no major changes in the analysis system over the 13-year period studied except for the change from the eighth to the ninth revision of the International Classification of Disease in 1978.

The Rotherham District Health Authority (DHA) has a resident population of approximately 250000. There is a particular interest in peptic ulcer disease in the Rotherham District General Hospital and consequently a greater use of H_2RA in the district compared with the Trent RHA area as a whole and with the national average. Therefore, the effect of this greater use on DU admission in this area has been separately examined.

An index of the volume of H_2RA used per year in the Trent RHA and in the Rotherham DHA was created, based on sales at constant prices. Though cimetidine was available on prescription from November 1976, accurate data on sales based on geographic locations were not available until 1978, which consequently has been used as the base year. However, *Figures 1–4*, which show the rising use of H_2RA, start from 1977, the first full year of cimetidine sales. Less was sold in this year than subsequently, although accurate regional sales data are not available. The lines on the graphs have been arbitrarily interpolated to reflect this fact. Ranitidine was introduced in October 1981; the volume sold since 1981 was converted to a cimetidine-price-equivalent. Thus the figures for the volumes of both drugs sold could be combined. The index reflects overall sales for the drugs and not specifically use related to DU as such information is not available. The data are up to 1983. Thereafter the method of recording sales changed and the use of H_2RA by region or town could not be accurately calculated. Nevertheless, the sales in 1984 exceeded those in 1983 and it is therefore presumed that the use of these drugs for DU is at least as great as in 1983. The H_2RA usage data were estimated with the assistance of the Market Research and Information Department, Smith Kline and French Laboratories Limited, UK.

Our data are presented in two ways. Firstly, a comparison is made of DU admissions for each category examined, before and since the availability of H_2RA: the average of the admission rate in the two periods is examined. Secondly, data are presented as a change in the yearly rate of admission throughout the two periods. This was done to see whether the rate of change in the H_2RA period was greater than in the pre-H_2RA period, in which case the treatment may reasonably be assumed to have a bearing on this change, or whether there was no difference in the rates when it must be assumed that any change due to drug treatment is no greater than that caused by a varying natural history of the disease.

For the Trent RHA data, we have compared the admissions in the years 1972–76, inclusive, with those in 1977–84. In Rotherham, however, cimetidine became available for experimental use in April 1976. We have therefore compared admissions in the years 1972–75 inclusive *versus* 1976–84. Furthermore, to examine the effect of the use of H_2RA on elective surgery, the latter period has been subdivided from 1976 to 1978 inclusive, when cimetidine was principally used intermittently[18], *versus* 1979 onwards when maintenance treatment with cimetidine[19,20], and to a much lesser extent with ranitidine[21], was commonly used and patients with refractory DU were treated with high-dose cimetidine if necessary[22]

Statistical methods

Differences between the mean admission rates in the pre-H_2RA period and H_2RA period were calculated for statistical comparison using the standard errors of the differences. The changes in yearly admission rates were examined by calculating the slopes of the weighted regression lines

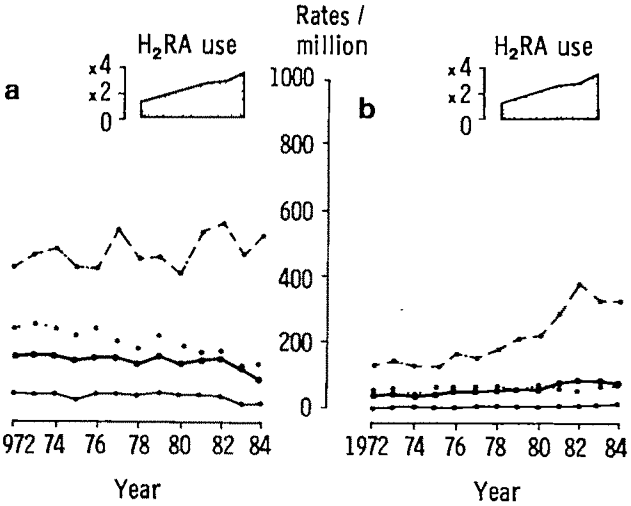

Figure 1 *Admission rates for* **a** *men and* **b** *women with perforated duodenal ulcer, subdivided by age, in the Trent Regional Health Authority, 1972–84. The total volume of H_2-receptor antagonists (H_2RA) used is shown, and is not subdivided by sex. The rise in the total volume of H_2RA used from 1978 to 1983 is shown. The base year is 1978 and the amount used is arbitrarily taken as 100. The increase, compared with 1978, is indicated. Thus, in 1983, 3·7 times more H_2RA was used. – – >65 years, . . 35–64 years, —— <35 years, —— all ages*

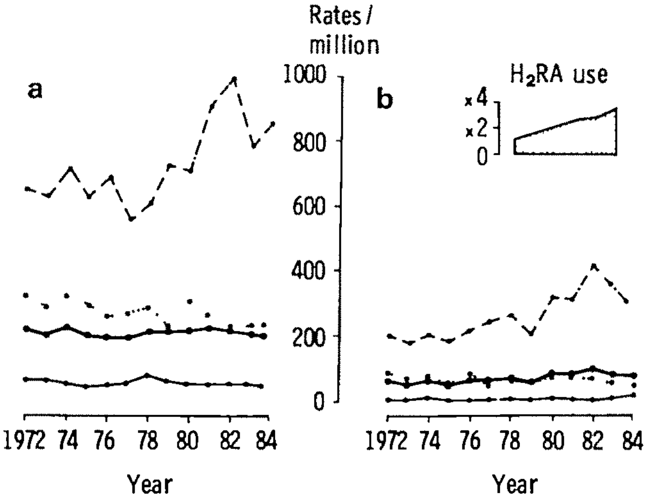

Figure 2 *Admission rates for* **a** *men and* **b** *women with bleeding duodenal ulcer, subdivided by age, in the Trent Regional Health Authority, 1972–84. The total volume of H_2-receptor antagonists (H_2RA) used is shown only in the graph on the right, and is not subdivided by sex. – – >65 years, . 35–64 years, ——<35 years, —— all ages*

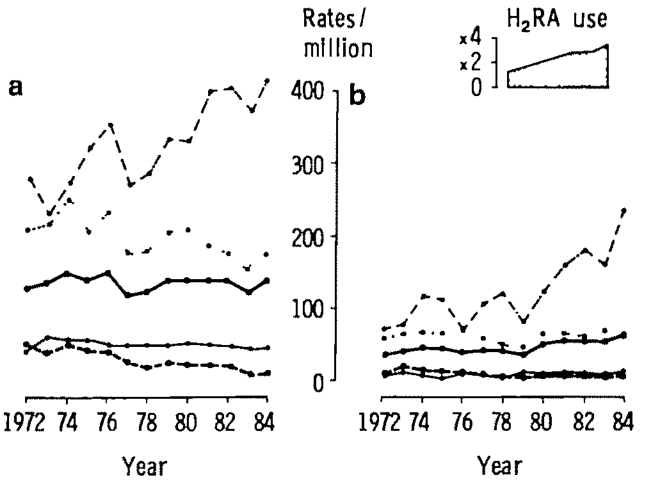

Figure 3 *Rates of emergency admission for* **a** *men and* **b** *women with uncomplicated duodenal ulcer, subdivided by age, and operation rates in the Trent Regional Health Authority, 1972–84 The volume of H_2-receptor antagonists (H_2RA) used is shown only in the graph on the right, and is not subdivided by sex. – – >65 years; . . 35–64 years, ——<35 years, —— all ages, – – – operations*

by the method of least squares[23] The level of significance adopted was three times or more the standard error, i e $P<0 01$

Results

In the Trent RHA the use of H_2RA in 1983 had risen by 3·7-fold compared with 1978, and in the Rotherham DHA the rise was 6·2-fold.

Changes in annual admission rates (per 10^6 of the population) in the Trent RHA: 1972–76 versus *1977–84* (Table 3)

Perforation (Figure 1). The overall annual admission rates for perforation have varied from 90 (in 1975) to 114 (in 1982) with a slight upward trend over the last 12 years on average 99 in the pre-H_2RA period compared with 103 thereafter ($P=0 06$). But these overall figures conceal a 33 per cent rise in the admission rates in people aged ≥65 years, from 264 to 352 ($P<0·01$), the rise being most marked in elderly women.

Haemorrhage (Figure 2). Haemorrhage occurred more frequently than perforation, the annual admission rates varying from 122 (in 1975) to 151 (in 1982) over the past 13 years. The rates have risen by 8 per cent, from 130 in 1972–76 to 140 thereafter ($P<0 01$) But in the elderly (≥65 years) there was a sharp rise of 28 per cent from 381 to 489 ($P<0·01$).

Uncomplicated DU admitted as an emergency (Figure 3) The annual admission rates have varied from 80 (in 1972) to 102 (in 1984) but the average admission rate for the two periods was similar: 88 in 1972–76 *versus* 89 in 1977–84. However, in those aged ≥65 years, the admission rate rose by 36 per cent, from 169 to 230 ($P<0·01$). Though admission rates did not change overall, the availability of cimetidine was associated with a dramatic fall of 58 per cent in the proportion of admitted patients who were operated on, from 30 per cent in the pre-H_2RA period to only 12 per cent thereafter, the operation rates per 10^6 of the population falling from 26 to 11 ($P<0·01$).

Uncomplicated DU admitted from the waiting list (Figure 4). The admission rates were falling even before cimetidine became available, and the reduction was most marked in middle-aged patients (35–64 years). But in the H_2RA era there was a further fall of 43 per cent, from 187 in 1972–76 to 106 in 1976–84 ($P<0·01$). The proportions of admitted patients who were operated on in these two periods also fell: 87 per cent *versus* 72 per cent respectively. The combined effect of the fall in admission and the fall in the proportions operated on resulted in the operation rates decreasing from 162 to 76, i e. by 53 per cent ($P<0·01$).

Uncomplicated DU admitted from the waiting list: changes in rates of admission and of operation (Table 4). The continued fall in admissions and operations in the H_2RA period occurred at a rate not significantly greater than in the years pre-H_2RA

Changes in annual admission rates (per 10^6 of the population) in the Rotherham DHA, 1972–75 versus *1976–84* (Figure 5)

Despite the fact that proportionately about 80 per cent more H_2RA are used in Rotherham than in the Trent RHA per head of population, there was no reduction in emergency admissions. Indeed, admission rates for uncomplicated DU patients admitted as emergencies in Rotherham rose by 40 per cent, from 130 in 1972–75 to 182 thereafter ($P<0·01$). However, the proportions of admitted patients requiring surgery in these two periods fell markedly by 70 per cent, from 20 to 6 per cent ($P<0 01$), the operation rates per 10^6 of the population declining from 27 to 10.

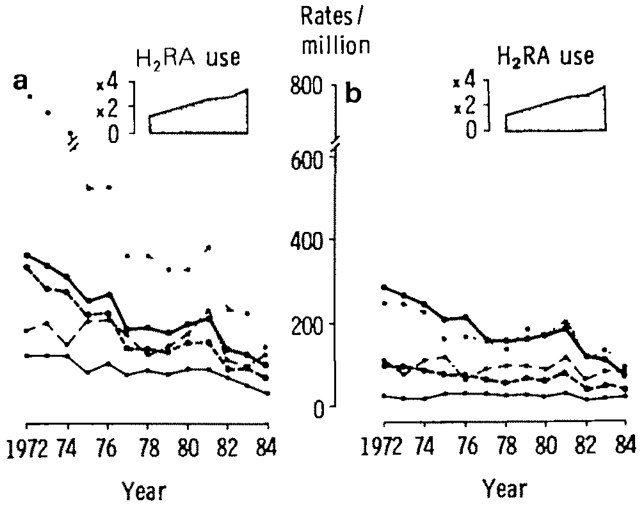

Figure 4 *Rates of admission for* **a** *men and* **b** *women, subdivided by age, from the waiting list, and operation rates in the Trent Regional Health Authority, 1972–84 The total volume of H_2-receptor antagonists (H_2RA) used is shown, and is not subdivided by sex – – >65 years, ... 35–64 years, ——<35 years, —— all ages, – – – operations*

Table 3 *Summary of the main changes in average annual admission and in annual operation rates per 10^6 of resident population in duodenal ulcer patients in the Trent Regional Health Authority*

	Period			
	1972–76 Pre-H_2RA period	1977–84 H_2RA period	Change	
Perforation (admission rates)				
All ages	98·5	102·6		
Age ≥65 years	263·8	351·6	↑33%	($P<0·01$)
Haemorrhage (admission rates)				
All ages	129·6	140·3	↑ 8%	($P<0·01$)
Age ≥65 years	380·7	488·7	↑28%	($P<0·01$)
Emergency admission (uncomplicated DU)				
Admission rates (all ages)	87·6	89·2		
Admission rates (≥65 years)	169·2	230·3	↑36%	($P<0·01$)
Proportions operated on	29·6%	12·3%		
Operation rates	26·0	11·0	↓58%	($P<0·01$)
Waiting list and booked admissions (uncomplicated DU)				
Admission rates (all ages)	187·0	106·2	↓43%	($P<0·01$)
Proportions operated on	87%	72%		
Operation rates	162·4	76·2	↓53%	($P<0·01$)

DU, duodenal ulcer. Data for men and women combined

Table 4 *Changes* in the annual rates of admission and in annual rates of operation in patients admitted from the waiting list, i.e. elective admissions and surgery*

		Admissions	P	Operations	P
Trent Regional Health Authority (excluding Rotherham)					
Pre-H_2RA	(1972–76)	−16·6	<0·01	−15·6	<0·01
H_2RA	(1977–84)	−7·4	<0·01	−6·0	<0·01
Overall	(1972–84)	−10·8	<0·01	−11·1	<0·01
Rotherham District Health Authority					
Pre-H_2RA	(1972–75)	−34·9	n.s.	−32·1	n.s
H_2RA	(1976–84)	−25·1	<0·01	−17·7	<0·01
Overall	(1972–84)	−29·3	<0·01	−26·5	<0·01

* The figures are the slopes of the weighted regression lines and represent changes per 10^6 resident population; n.s , not significant at the 5 per cent level

The most striking change, however, has been in the reduction in admissions from the waiting list and in the proportions requiring elective operation. The admission rates in the three periods 1972–75, 1976–78 and 1979–84 were, respectively, 353, 251 and 97 The proportions of these patients who were then operated on were 74, 53 and 25 per cent respectively, the operation rates per 10^6 of the population for the three periods being 262, 132 and 24. Thus, compared with the pre-H_2RA period (1972–75), in 1976–78 (when H_2RA were used mainly intermittently) and in 1979–84 (when maintenance and high-dose H_2RA therapy was commonly used) admission rates fell by 29 and 73 per cent respectively. This fall, in conjunction with the reduced proportion of patients operated on, led to a fall in elective surgery of 50 and 91 per cent in the two periods respectively.

The reduction in elective admissions and of operation rates in the pre-H_2RA period was not significant, whereas in the H_2RA period the decline was highly significant (*Table 4*).

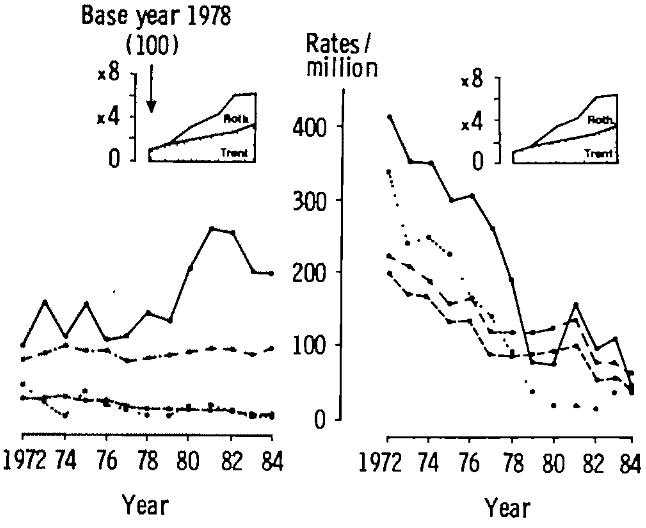

Figure 5 *Comparison of admission and operation rates in patients with uncomplicated duodenal ulcer in the Trent Regional Health Authority (RHA) and in the Rotherham District Health Authority (DHA), 1972–84, and the effect of differing H_2-receptor antagonist (H_2RA) usage The graph on the left shows emergency admissions, and that on the right shows admissions from the waiting list. The admission data here are not divided by sex and age. The volume of H_2RA used in the Trent RHA is the same as in the previous figures, the additional use in the Rotherham DHA is represented by the unstippled portion —— Rotherham admissions, –·– Trent admissions, . . . Rotherham operations, --- Trent operations*

Discussion

Despite the increasing use of H_2RA in the Trent RHA, there has been no reduction in admission rates in patients with DU complicated by perforation or by haemorrhage, nor in patients with uncomplicated DU admitted as emergencies; indeed, admission rates have risen in the elderly, particularly in women Neither has there been a reduction in Rotherham, where the increase in the use of H_2RA has been even more marked. In fact, the true incidence of perforation and haemorrhage is likely to be greater than the admission rate, for several such patients die suddenly at home from their complications and therefore are not included in admission statistics[24]. In contrast, admissions from the waiting list and in the proportions of such patients operated on have fallen; this decrease has been more marked in Rotherham and may be connected with the greater intensity with which the H_2RA are used

It is difficult to be certain why emergency admissions have not declined but at least three factors contribute. Firstly, many patients have no prior ulcer history or have not been investigated for their dyspepsia. Secondly, even in patients known to have DU, there may be few or no heralding symptoms and the first manifestation of an ulcer recurrence is haemorrhage, perforation or violent pain. Thirdly, with the increasing use of non-steroidal anti-inflammatory drugs in the elderly, a higher proportion of patients become vulnerable to developing ulcer disease and its complications[25]. In the first two instances, there is no opportunity to intervene with a healing course of H_2RA. Probably the only way of reducing such admissions is to use maintenance therapy to decrease ulcer relapse rates[26] but this would be applicable only to patients with known duodenal ulcer disease.

The striking fall in elective admissions, and hence in elective surgery, started long before the H_2RA became available and presumably is due (at least in large part) to changes in the natural history of the disease This decline has continued in the H_2RA era. In the absence of controlled studies (which would be impractical), it is difficult to determine how much of this further decline is due to the changing natural history and what proportion can be attributed to elective modern treatment. In the Trent RHA the continued decline during the H_2RA period is at a rate not significantly greater than in the preceding period, suggesting that the increasing use of these powerful drugs did not necessarily have a decisive effect, certainly no greater than that produced by a changing natural history. In the Rotherham DHA, however, the rate of decline in elective admissions and operations in the pre-H_2RA period was not significant, whereas the intensive use of these drugs has been associated with a significant fall (although as the number of patients involved is small, some caution is needed in interpreting these data).

Despite our failure to find a distinct effect of the H_2RA on elective admissions and operations in the Trent RHA, it is hard to believe that such effective therapy does not have any impact: it is common experience that patients who today (and in the past few years) would undoubtedly have been recommended for elective operation can instead be managed medically. Indeed, perhaps it is the alternative to operation offered by H_2RA therapy in many patients that explains, in part, the varied elective surgery rates, reflecting how the choice is exercised (see below).

The explanations that perhaps best fit our observations are that elective admission and surgery have declined dramatically because of a changing natural history; that widespread use of the H_2RA (as in the Trent RHA) has an added effect but one not so large as to be statistically discernible; that intensive use (as in the Rotherham DHA) has a definite additional effect; and that it is the level of intensity of use that determines whether any decline is greater than that produced by a changing natural history

To put our results in perspective, it is pertinent to point out that the lack of overall change in the admission rate for perforation in this study must be compared with the UK admissions, which have been declining over the past 20–30 years[1–3,27]. However, the results from individual centres and from regions are more variable. Several centres have reported an unchanged rate[28–32], one a rising rate[33], and two the opposite[34,35]. Less information is available concerning admissions for haemorrhage except in one centre where admissions fell despite an unchangd rate for perforation[28] Such a variable picture is also seen outside the UK. Various surveys in the USA have reported a reduction in admissions for haemorrhage and perforation[4,5,8], although some centres have not observed any change[9] or have noted an increase in perforation rates (but not haemorrhage)[10] Centres in western Europe have reported admission rates for perforation which are unchanged[36–38,50], decreased[39–41], or even increased[42,43]; in Hong Kong[44,45] there has been a sharp increase. In Athens, admission rates for gastrointestinal bleeding have remained unchanged[46], and in Finland they have increased[38].

Reductions in elective admissions and surgery have also been variable. In the UK, admission rates have steadily fallen since 1968 and the fall has continued since cimetidine became available[1,3]. The reduction in individual centres, however, has been variable and the figures quoted include almost nil[33], 28 per cent[30], 30 per cent[32], 38 per cent[28,29], 39 per cent (with a range of 2–67 per cent)[47] and 70 per cent[34]. A similar pattern has been seen in the USA[4,5,8–14,48] and in western Europe[15,16,36–41,43,49] In contrast, one centre in Australia reported no change[51], and in Hong Kong there has actually been a rise[44,45].

It is difficult to determine why there is such a variation in admission and surgical rates. For perforation and haemorrhage, presumably geographical variation in aggressiveness of ulcer disease, life-style changes, use of anti-inflammatory drugs and other changes in the natural history are the principal determinants. For elective admissions and surgery, however, the way in which H_2RA are used and the criteria to select patients for operation may prove the major determinants. The main indication for elective surgery remains 'failed medical treatment' but how this is defined varies considerably and there are not sufficient studies to relate selection policy directly to the numbers of patients undergoing operation. However, it is common knowledge that in some centres patients are selected if they relapse 2–3 times after healing treatment is stopped. As H_2RA are effective only for the duration they are used, this criterion is unlikely to have much effect in reducing operation rates[52]. In contrast, others prefer to select only patients who relapse on maintenance treatment. Indeed, Venables[53] predicted that such a selection process would reduce operation rates by 58 per cent and in an earlier report observed that in his region it fell by 57 per cent; but others have found that maintenance treatment does not always reduce operation rates as much as expected[54]. In Rotherham we use low-dose maintenance treatment with 400 mg cimetidine nightly (or with 150 mg ranitidine nightly); in those who repeatedly relapse, we use maintenance treatment with 1 g cimetidine (or 0·3 g ranitidine) daily. Elective surgery is now used principally in patients with troublesome refractory duodenal ulcer, i.e. the ulcer remains active (as proved by endoscopy) and causes severe symptoms despite healing treatment with cimetidine at doses of 2 g or 3 g (or with 0·6–0·9 g ranitidine) given for at least 3 months, plus antacids up to 1000 mmol daily; if out-patient treatment fails, we attempt in-patient treatment[22] We suspect that it is the vigorous use of H_2RA which, at least in part, is responsible for the marked reduction in elective surgery in this centre. We have no reason to suspect our patients have milder disease than anywhere else in the UK; indeed, our operation rates in the pre-H_2RA period were considerably higher than for the Trent RHA, despite a lower surgical staffing, which suggests that if anything the disease here may be more aggressive. To put the Rotherham data into perspective, in 1972–75 (pre-H_2RA) on average 60 elective vagotomy and drainage operations were done each year In 1976–78 (when intermittent treatment was used) 42 operations were performed. In 1979–84, when H_2RA were used vigorously, operation rates fell to nine per year.

It has commonly been assumed that the decrease in surgery seen shortly after H_2RA became available was only temporary, that operation was merely being postponed rather than prevented However, over the following years there has been no 'rebound'. Our observations in Rotherham are that some patients who were once well-controlled medically go on to develop refractoriness and ultimately need surgery But such examples are few and are more than offset by the far larger number of people for whom modern medical treatment provides an effective alternative to surgery

There is a feeling that the rising perforation and haemorrhage rates in the elderly represent the consequence of failing to operate electively, and hence curatively, on these patients in their earlier years and instead relying on medical treatment which merely suppresses the disease. Our data do not allow us to draw any conclusions on this point The H_2RA have been widely available only since 1977. Certainly patients who were in their late 50s or early 60s several years ago and were treated medically instead of by definitive surgery could now present with complications and hence add to the rising rate of haemorrhage and perforation in those aged over 65 years. However, this explanation cannot apply to young patients in this study for, even if they developed complications later on, they would still be aged under 65 years, a group in which the complication rate is falling

Recently, the mucosal protectant, colloidal bismuth, has been found to be effective in healing refractory duodenal ulcer[55,56], as has the experimental compound omeprazole, which is perhaps the most powerful antisecretory drug available[57]. These drugs may lead to still further reductions in surgery, although it is extremely unlikely that medical treatment will ever be a complete alternative to elective surgery. It remains to be seen whether the vigorous—perhaps over-vigorous—use of H_2RA in reducing elective surgery is economic or indeed even desirable; for younger patients one approach may be to use the H_2RA to begin with but to go on to early elective surgery in those in whom 'standard treatment' fails[58].

Many doctors are sceptical of the accuracy of the Hospital Activity Analysis, on which our data are based. For logistical reasons, we were unable to check random samples of notes from different hospitals for accuracy in coding other than in Rotherham, where the error rate was low even before the survey began However, an important study on the accuracy of the Hospital Activity Analysis in the Trent RHA comments: 'We feel that the mistrust frequently expressed by consultants in the information produced from Hospital Activity Analysis should be directed towards the quality of the original medical notes than to the Hospital Activity Analysis system itself which, from the results of the study, seems to be quite a good reproduction of what is contained in them.'[59]. Since this survey was done, further efforts have been made in the Trent RHA to improve accuracy; as all coding clerks in the region work to the same specification, variation in error rate is probably small One source of error is confusion between DU and 'peptic ulcer, site unspecified'. However the number so classified is small and misclassification is unlikely to affect our findings. We took the precaution of surveying only easily identifiable diagnoses and of grouping all antiulcer operations. Thus, by using broad headings, errors through misclassification will have been minimized.

In conclusion, we have found that even a marked increase in the use of H_2RA does not diminish emergency admission rates in patients with DU, with or without complications. In contrast, the increase is associated with a decrease in elective admissions and hence in elective surgery. In the Trent RHA, where the use of H_2RA has risen 3·7-fold, the effect of therapy cannot clearly be distinguished from that produced by changes in the natural history of the disease; but in the Rotherham DHA, where the drug use has increased 6·2-fold, there has been an acceleration in the decline, presumably the consequence of the drug treatment.

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A clinicopathological study of synchronous multiple gastric cancer

T. Mitsudomi,
A. Watanabe,
T. Matsusaka, Y. Fujinaga,
T. Fuchigami and
A. Iwashita

Departments of Surgery,
Gastroenterology and Pathology,
Matsuyama Red Cross Hospital,
Matsuyama 790, Japan
Correspondence to:
Dr T. Mitsudomi, Department of
Surgery II, Faculty of Medicine,
Kyushu University, Fukuoka 812,
Japan

In a 7½-year period (from 1 January 1980 to 30 June 1987), 997 patients with gastric cancer underwent gastric resection at the Department of Surgery, Matsuyama Red Cross Hospital, Japan. We studied clinicopathologically 83 patients (182 lesions) with synchronous multiple gastric cancer and compared them with patients who had solitary cancers only in the same period. We found that elderly men had a relatively high incidence of multiple gastric cancer, and that early cancer of the elevated well differentiated type was the most common. Of the 182 lesions, as many as 42 (23·1 per cent) were missed in the preoperative examination. Eighteen of these 42 lesions were found only with the aid of a microscope in sections almost incidentally excised. Small flat lesions tended to be missed. We should always be conscious that other gastric lesions may be present when treating patients with gastric cancer.

Keywords: Multiple gastric cancer

Malignancy is a leading cause of death and gastric cancer is the commonest malignancy in Japan. The incidence of synchronous multiple gastric cancer is variously reported to be 2·07 per cent[1], 5·22 per cent[2], 6·5 per cent[3], or 8·6 per cent[4] and has been increasing recently, probably with advances in the diagnosis of gastric cancer.

Multiple gastric cancer causes several problems in both the diagnosis and the therapy of gastric cancer. Some of these lesions are not suspected before operation and are found almost by chance during histological examinations after surgery performed only to remove the main lesion. How can we reduce the incidence of missed lesions? Are there any clinicopathological characteristics related to the multiplicity of gastric cancers? To seek answers to these questions, we conducted a retrospective study of 83 consecutive patients with multiple gastric cancer encountered at the Matsuyama Red Cross Hospital from 1 January 1980 to 30 June 1987.

Patients and methods

During the 7½ years from 1 January 1980 to 30 June 1987, 1110 patients with histologically diagnosed gastric cancer were treated at the Department of Surgery, Matsuyama Red Cross Hospital Most of these patients were inhabitants of Ehime Prefecture, Japan. Of these, 997 patients underwent gastrectomy (resection rate 89 8 per cent) and their case notes have been reviewed

There were 83 patients (8·3 per cent) with synchronous multiple gastric cancer and the total number of cancerous lesions in these patients was 182 (72 double, nine triple, one quadruple, and one septuple) The diagnostic criteria for synchronous multiple gastric cancer were essentially those of Moertel *et al.*[1]: (1) each lesion must be of pathologically proved malignancy, (2) all lesions must be separated by intervals of microscopically normal gastric wall; (3) the possibility that one of the lesions represents a local extension or metastatic tumour must be ruled out beyond any reasonable doubt

These cases were evaluated with respect to age and sex, macroscopic type, histological type, lymphatic and venous invasion, accompanying benign lesions, stage, missed lesions, operation performed, and outcome They were compared with 914 patients with solitary gastric cancer operated on during the same period The clinical diagnosis of gastric cancer was made by multiple examinations using barium upper gastrointestinal series and endoscopy, usually with dye spraying and biopsy

Resected stomachs were routinely opened intraoperatively and examined macroscopically by surgeons After fixation with 10 per cent formalin, they were again examined macroscopically by a pathologist and were cut into strips (5 mm in width) for microscopic examination. The strips were taken from the area around the macroscopically suspected lesions. Long strips along the long axis of the stomach were usually taken to determine whether oral and aboral stumps of the resected stomach were free from cancer cells

Clinicopathological descriptions of gastric cancer, including macroscopic classification of early cancer, were based on the General Rules for Gastric Cancer Study in Surgery and Pathology in Japan[5] Statistical evaluation employed the χ^2 test and the generalized Wilcoxon test. Survival rates were calculated by the Kaplan–Meier method.

Results

Of the 83 patients with multiple gastric cancer, 42 had only early gastric cancers (with infiltration limited to either the mucosa or the submucosa, irrespective of lymph node metastasis), six had only advanced cancers, and 35 had both early and advanced cancers. The 83 patients had 182 cancerous lesions in total, of which 134 (73·6 per cent) were early gastric cancers. This rate was significantly higher than that in the 914 patients with solitary cancers, 388 (42·5 per cent) of whom had early lesions ($P<0·01$). An examination of the data on the basis of number of patients also indicates that the patients with multiple cancers had less advanced lesions than those with solitary cancers ($P<0·01$).

Age and sex

The average age of the patients with multiple gastric cancer was 64·2 years and 60·3 years in those with a solitary lesion. This difference was statistically significant ($P<0·01$). As shown in *Figure 1*, the incidence of multiple gastric cancer increased with age. In the group with multiple cancer the male:female ratio was 59:24 (2·46:1), which was higher than the ratio of 601:313 (1·92:1) in the group with solitary cancers ($P<0·01$)

Site

In the patients with multiple cancers the proportion of lesions located in the lower, middle, and upper thirds of the stomach was 54·4, 33·5, and 12·1 per cent, respectively. The values for those with solitary cancers were similar, namely 49·3, 36·7, and 13·0 per cent respectively.

Macroscopic classification of the early lesions (Table 1)

When early gastric cancer was classified macroscopically, the most common type was IIc (superficial depressed) in both groups. The elevated type of gastric cancer occurred more frequently in the multiple group ($P<0·01$).

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Histological examinations

Differentiated adenocarcinoma (or intestinal type according to Lauren[6]) comprised 49·1 per cent of the cancers in the solitary group and 76·9 per cent of the cancers in the multiple group. This difference was statistically significant ($P < 0{\cdot}01$). In the multiple group, 57 patients had only differentiated lesions, 12 patients had undifferentiated lesions, and 14 patients had both differentiated and undifferentiated lesions. In 11 of these 14 cases, the undifferentiated lesions infiltrated deeper than the differentiated ones.

Lymphatic and venous invasion

It is sometimes difficult to verify Moertel's third criterion for multiple gastric cancer, which states that the possibility that one of the lesions represents a local extension or metastatic tumour must be ruled out[1]. To examine the possibility that the accessory lesion(s) resulted from a spread of the main lesion through lymphatic or venous channels, we compared the lymphatic and the venous invasion by cancer cells in the two groups. Invasion into lymphatic channels appeared in 49·9 per cent and 41·0 per cent of the solitary and multiple groups, respectively. Venous invasion was observed in 25·4 per cent of the solitary group and 27·7 per cent of the multiple group These differences were not statistically significant ($P > 0{\cdot}05$ in both cases).

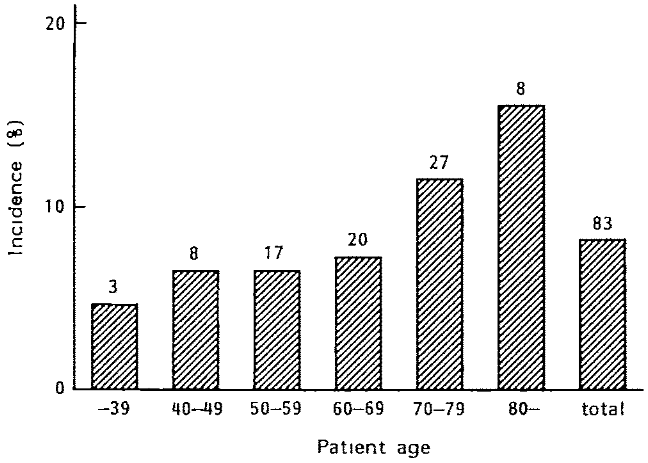

Figure 1 *Relative increase in multiple gastric cancer in each decade. The figure on each column shows the number of patients*

Accompanying benign lesions

There were 15 multiple gastric cancer patients with benign peptic ulcer and 20 of their 31 cancerous lesions were of the depressed type. On the other hand, 13 of 16 lesions from seven patients with adenoma were of the elevated type.

Stage

There was a tendency for the histological stage to be earlier (i.e. stage I or II) in the multiple group than in the solitary group ($P < 0{\cdot}01$) (*Table 2*).

Missed lesions

Forty-two lesions (40 early cancers and two advanced cancers) were missed before operation (*Table 3*). The average diameter of these was 1·01 cm Eighteen of them from 16 cases were not suspected even in the postoperative macroscopic examination but were found histologically in sections taken and examined by chance. These 18 lesions had an average diameter of 0·49 cm and were all intramucosal cancers except for one lesion with submucosal infiltration. The average size of the other 24 missed lesions, which were found in the intraoperative or postoperative macroscopic examination, was 1·41 cm. This was significantly larger ($P < 0{\cdot}01$) than the 0·49-cm average size of lesions found microscopically and was obviously smaller than the 3·94-cm average size of the 115 lesions diagnosed preoperatively

Table 1 *Macroscopic classification of the early lesions in patients with solitary and multiple gastric cancers*

	Elevated			Flat	Depressed			Combined	Not examined
	I	IIa	Other	IIb	IIc	IIc+III	Other		
Solitary	12	30	5	1	231	48	16	42	3
Total		47 (12·1)				295 (76·0)			
Multiple	12	31	3	6	62	5	1	14	
Total		46 (34·3)				68 (50·7)			

The values in parentheses are percentages

Table 2 *Stage distribution of patients with solitary or multiple gastric cancers*

	Stage I	Stage II	Stage III	Stage IV
Solitary	442 (48·4%)	120 (13·1%)	193 (21·1%)	159 (17·4%)
Multiple	52 (62·7%)	16 (19·3%)	8 (9·6%)	7 (8·4%)

Table 3 *Macroscopic classification of lesions not diagnosed before operation*

	Early				Advanced
	Elevated IIa	Flat IIb	Depressed IIc	Combined	
Lesions found macroscopically	6	1	12	3	2
Lesions found microscopically	5	5	8	0	0

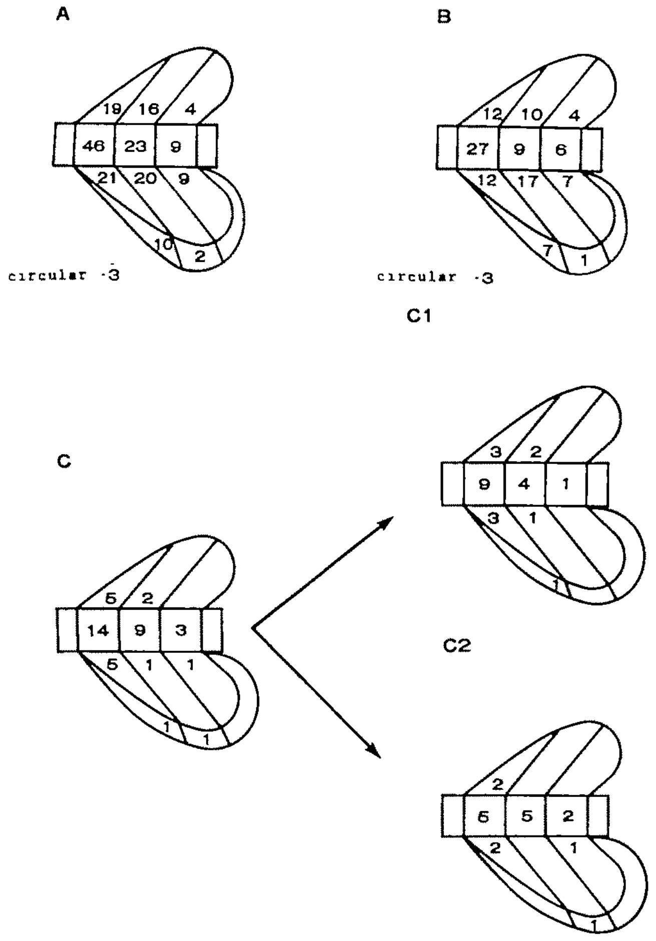

Figure 2 *Distribution of the multiple cancerous lesions in the stomach A distribution of all lesions (n = 182, average diameter $\bar{x} = 2\cdot94$ cm), B distribution of lesions diagnosed preoperatively (n = 115, $\bar{x} = 3\cdot94$ cm), C distribution of lesions missed in preoperative examination (n = 42, $\bar{x} = 1\cdot01$ cm), C1. distribution of group C lesions found macroscopically during or after operation (n = 24, $\bar{x} = 1\cdot41$ cm), C2: distribution of group C lesions found on postoperative histological examination (n = 18, $\bar{x} = 0\cdot49$ cm)*

($P < 0\cdot01$). The distributions of the lesions from these groups are shown in *Figure 2*. There was no apparent difference between the groups in terms of location of the tumours.

Twelve lesions were not detected by upper gastrointestinal radiology but were detected by endoscopy. Ten of these 12 lesions were located on the anterior wall or the lesser curvature of the stomach. Only one lesion was detected solely by barium upper gastrointestinal study.

A macroscopic classification of the missed lesions is shown in *Table 3*. Compared with *Table 1* data, the incidence of flat-type early cancer was high in the group of lesions found microscopically ($P < 0\cdot01$).

When the site of each lesion was assigned to 12 regions of the stomach as shown in *Figure 2*, missed lesions in six cases were located more proximally in the stomach than were lesions diagnosed preoperatively However, in only one case was the operation modified from partial resection to total gastrectomy because of the intraoperative discovery of the new lesions. In another case, the proximal resected margin was not free of cancer cells because the lesion was missed until the postoperative histological examination. However, postoperative examination revealed no residual lesion and the patient is well without sign of recurrence 2½ years after surgery

Operations

It is possible that the larger the proportion of stomach that is removed, the higher the incidence of multiple gastric cancers. However, the frequency of total gastrectomy did not differ significantly between the two groups (28·1 per cent in the solitary group and 32·5 per cent in the multiple group). The 3-year and 5-year survival rates with respect to type of operation, stratified according to histological stages, are shown in *Table 4*.

Outcome

The 5-year survival rate calculated by Kaplan–Meier's method for multiple gastric cancer patients was 72·6 per cent, which is not significantly different from the rate of 66·0 per cent for those with solitary cancer.

Discussion

We have shown that patients with multiple gastric cancer have several clinicopathological characteristics which differ from those of patients with solitary cancer; in particular, elderly men had a relatively high incidence of multiple cancer and early cancer of the elevated, well differentiated type was most common. These characteristics have been noted previously[2,4] although Noguchi *et al.*[3] reported that there was no difference in the macroscopic type while noting preponderance of male and older patients in the group with multiple gastric cancer

Well differentiated cancer of the elevated type is characteristic of gastric cancer in the elderly[7–9]. Intestinal metaplasia becomes predominant with ageing[10,11] and well differentiated carcinoma arises from this metaplasia[6,11,12]. Furthermore, metaplastic mucosa is more prone to oncogenesis than ordinary mucosa[13]. These facts at least partly explain the above relationship between multiple gastric cancer and the elderly The possibility that synchronous multiple gastric cancers fuse together after both vertical and horizontal growth to form a single advanced cancer may explain the high incidence of early cancer in the patients with multiple gastric cancer, as suggested previously[14].

Forty-two lesions out of the 182 (23·1 per cent) in the present study were never suspected in the preoperative examinations. Furthermore, 18 of these 42 lesions were not detected in the postoperative macroscopic examination. Size and macroscopic type of lesion appear important in that the smaller the lesion the greater was the chance of missing it and the flatter the lesion the harder it was to find. We could not detect a trend in the site distribution of the missed lesions, although barium meal studies were less sensitive than endoscopy for lesions located on the anterior wall and lesser curvature of the stomach. At present, we have to admit that it is difficult to diagnose these minute flat carcinomas found only with the aid of the microscope. New methods for the diagnosis of gastric cancer, such as electronic endoscopy with image processing or *in vivo* specific staining of cancerous lesions are awaited with interest. Intraoperative cytology or frozen section diagnosis may also reduce the incidence of missed lesions.

Table 4 *Three-year and 5-year survival rates with respect to type of operation stratified according to histological stage*

Stage	Operation	3-year survival rate (%)	5-year survival rate (%)
I	PG	97·4	97·4
	TG	87·7	87·7
II	PG	87·0	87·0
	TG	74·0	55·5
III	PG	56·0	44·4
	TG	45·3	31·3
IV	PG	13·4	11·2
	TG	9·2	2·3

PG, partial gastrectomy; TG, total gastrectomy

We can reduce the likelihood of missing macroscopic lesions by always bearing in mind the possibility that multiple gastric cancer can occur at any time, especially when diagnosing gastric cancer in aged, male patients with elevated lesions. We should remember that the prevalence of multiple gastric cancer is one out of 12 patients with gastric cancer. The present study also leads us to suspect that undetected minute cancer may exist in the stomach remnants in several patients. However, we have not often encountered gastric cancer arising from the remnant stomach. Furthermore, survival after total gastrectomy does not exceed that after partial gastrectomy when allowance is made for histological stages (*Table 4*) and the quality of life is usually better sustained after partial gastrectomy than after total gastrectomy. Optimistically, there may be spontaneous regression of the cancer in its very early stage, although we do not have data to support this concept. For these reasons, we do not favour a policy of elective total gastrectomy for any patient with gastric cancer. However, it should be emphasized that careful postoperative follow-up is essential to detect any missed lesion(s) in the remnant stomach.

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Determinants of gastro-oesophageal reflux and their inter-relationships

F. Johnsson,
B. Joelsson and
K. Gudmundsson

Department of Surgery,
Lund University, S-221 85 Lund,
Sweden
Correspondence to:
Dr F Johnsson

Gastro-oesophageal reflux was measured by 24-h ambulatory oesophageal pH monitoring in 220 patients with symptoms suggestive of gastro-oesophageal reflux disease. By multiple regression analysis it was found that the pressure in the distal oesophageal high pressure zone, the presence of a hiatal hernia, the intra-abdominal length of the high pressure zone, the amplitude of the contraction waves in the distal oesophagus and age all significantly participated in the determination of the amount of gastro-oesophageal reflux. The pressure in the distal oesophageal high pressure zone was the single variable that correlated most strongly to the amount of reflux. Although the amount of reflux increased significantly with increasing weight as measured by Broca's index, this variable did not participate in the determination of reflux by the multiple regression test. The study emphasizes the role of the pressure and intra-abdominal length of the distal oesophageal high pressure zone as the primary antireflux barrier. It also shows that a hiatal hernia plays a role in generating gastro-oesophageal reflux through a mechanism other than affecting the pressure and the intra-abdominal length of the high pressure zone.

Keywords: Gastro-oesophageal reflux, 24-h pH monitoring, distal oesophageal high pressure zone, hiatal hernia, age, Broca's index, smoking, alcohol consumption

The pathophysiological mechanisms in gastro-oesophageal reflux disease have been thoroughly investigated. In the past the presence of a hiatal hernia was considered the main aetiological factor[1]. During the last 20 years, the finding of a hypotensive lower oesophageal high pressure zone has been said to be responsible for reflux disease[2–5]. Other contributing factors often discussed are the length of the high pressure zone (total and intra-abdominal) and the motor function of the oesophagus[6]. To what extent parameters such as age and weight, smoking habits and alcohol consumption affect the amount of reflux has been less frequently reported.

In the present study we have investigated the correlation between these variables and the amount of gastro-oesophageal reflux as measured by 24-h ambulatory pH monitoring in the oesophagus. Furthermore, using a multiple regression test, the relative importance of each variable in determining the amount of reflux has been analysed.

Patients and methods

We have studied 220 patients, 91 women and 129 men, with a median age of 49 years (range 17–75). They were consecutively referred to our oesophageal laboratory because of symptoms suggestive of gastro-oesophageal reflux disease and underwent oesophagogastroduodenoscopy, oesophageal manometry and ambulatory 24-h oesophageal pH monitoring. None had had previous gastric or oesophageal surgery, or had active gastric or duodenal ulcer. Before the investigations, the patients were interviewed about the number of cigarettes they smoked per day and their alcohol consumption. The weight of the patients was expressed as Broca's index· weight in kilograms divided by (height in centimetres minus 100)

Oesophagogastroduodenoscopy was performed with a flexible endoscope after topical anaesthesia of the pharynx. A hiatal hernia was diagnosed if the distance between the diaphragmatic crus and the tubular oesophagus exceeded 2 cm with the patient breathing quietly and with a non-inflated stomach Erosions or ulcerations in the distal oesophagus were found in 67 patients

Oesophageal manometry was performed with a three-lumen water-perfused catheter connected to an Arndorfer (Arndorfer Medical Specialties, Inc, USA) hydrocapillary pump. The catheter had three distal side-holes at 5-cm intervals differing 120 degrees in radial orientation. The stationary pull-through technique was used[7] The catheter was introduced nasally and positioned with all three side-holes in the stomach, it was then pulled back at 1-cm increments. The pressure, total length and intra-abdominal length of the distal oesophageal high pressure zone were calculated as the mean value from the three lumens of the catheter. The pressure was measured end-expiratory at the respiratory inversion point, referring to gastric pressure as zero. The length of the high pressure zone below the respiratory inversion point was considered to be the functional intra-abdominal length. The mean amplitude of the oesophageal contraction waves at dry swallows in the distal 5 cm of the oesophagus was also calculated.

Ambulatory 24-h pH monitoring was performed using portable pH-monitoring equipment (Synectics, Sweden) which consisted of a monocrystal-line antimony pH electrode, a silver–silver chloride reference electrode and a solid state memory box. After calibration at pH 7 and 1 the pH electrode was introduced nasally and placed with the pH recording tip 5 cm above the oral margin of the distal oesophageal high pressure zone previously located by manometry. The reference electrode was placed on the chest and the memory box was worn in a waist-belt The patients were instructed to lead as normal a life as possible and to take normal meals with the exception of acid food and beverages. Medication against gastro-oesophageal reflux such as H_2-blockers and metoclopramide was withdrawn 1 week and antacids 1 day before the investigation. After the monitoring period the data were analysed by a computer program (Esophogram, Gastrosoft, USA) on an IBM personal computer. The amount of gastro-oesophageal reflux was expressed as the percentage of time during the monitoring when pH was <4 in the oesophagus

Statistical methods

Spearman's rank correlation and multiple regression analysis were used[8] $P<0 05$ was considered statistically significant

Results

Correlations between the different variables and the amount of reflux and the results of multiple regression analysis are shown in *Table 1*. Multiple regression analysis allows a multi-dimensional regression between the variables. In other words, it is possible to determine the combination of variables

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Table 1 *Correlation between different variables and amount of reflux found by 24-h pH monitoring and the results of multiple regression analysis*

	r	m_r
HPZ. pressure	−0·52	0·167*
Hiatal hernia	0·33	0·190*
Broca's index	0·31	0·199
HPZ· intra-abdominal length	−0·30	0·235*
Contraction amplitudes in the distal oesophagus	−0·18	0·249*
Age	0·12	0·262*
HPZ total length	n s.	0·262
Smoking	n.s.	0.262
Alcohol consumption	n.s.	0·266

r, correlation coefficient according to Spearman's rank correlation in 220 patients, given for the statistically significant correlations ($P < 0·05$), m_r, coefficient of determination derived via the multiple regression analysis for the variable together with the preceding variables in the table; * statistically significant increase in determination ($P < 0·05$); HPZ, distal oesophageal high pressure zone

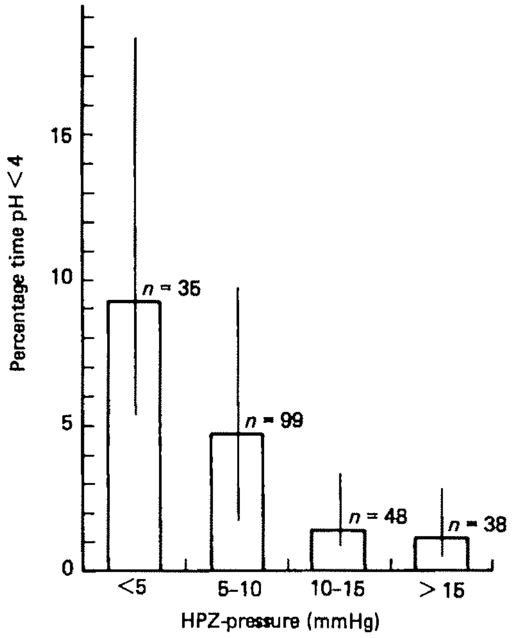

Figure 1 *Relation between pressure in the distal oesophageal high pressure zone (HPZ) and percentage of time with pH < 4 by pH monitoring Median and interquartile range. Spearman rank correlation r = −0·52, P < 0·001*

that together may explain the variation in amount of gastro-oesophageal reflux and to exclude those variables that do not contribute to this explanation. The pressure in the distal oesophageal high pressure zone, the presence of a hiatal hernia, the intra-abdominal length of the high pressure zone, the amplitude of the distal oesophageal contractions and the age of the patient each contributed significantly to this multiple regression. Broca's index, the total length of the high pressure zone, smoking and alcohol consumption did not.

The pressure in the distal oesophageal high pressure zone exhibited the strongest correlation to the amount of reflux (*Figure 1*). The intra-abdominal length of the high pressure zone (*Figure 2*), the presence of a hiatal hernia (*Figure 3*), the contraction amplitude in the distal oesophagus (*Figure 4*), Broca's index (*Figure 5*) and age (*Figure 6*) also correlated significantly to the amount of acid reflux. No significant correlation was found between reflux and the total length of the distal oesophageal high pressure zone, smoking or alcohol consumption.

Discussion

We have shown that the pressure in the distal oesophageal high pressure zone was the single factor that best correlated to the amount of reflux in our patients. Many published studies emphasize the role of the pressure in the high pressure zone as the major antireflux barrier[2–5]. There is evidence that this pressure may not always be related to the competency of the cardia[9]. There is a marked overlap in pressure between normal controls and patients with reflux[10] and the administration of atropine, which reduces the pressure of the high pressure zone, does not increase the indicence of reflux in normal subjects[11]. These findings have led to the suggestion that other factors also are involved in the antireflux mechanism[6]. As shown by multiple regression analysis in the present study, there are other factors that contribute to the determination of the amount of reflux. This means that these factors each influence reflux in a way that cannot be explained by their influence on the pressure of the distal oesophageal high pressure zone. The portion of the high pressure zone below the respiratory inversion point is subjected to changes in the intra-abdominal pressure[12] and an inadequate intra-abdominal portion leads to incompetence[13,14] A short overall length of the high pressure zone has also been cited as causing gastro-oesophageal incompe-

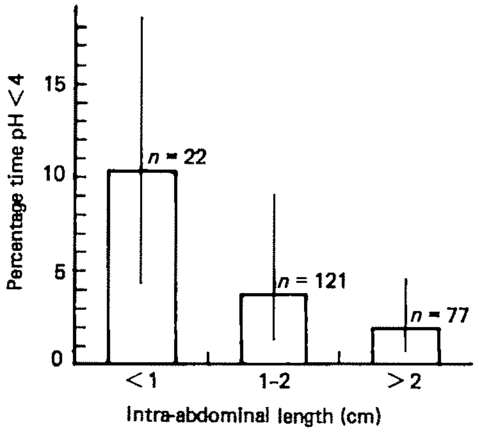

Figure 2 *Relation between intra-abdominal length of the high pressure zone and percentage of time with pH < 4 by pH monitoring Median and interquartile range. Spearman rank correlation r = −0·30, P < 0·001*

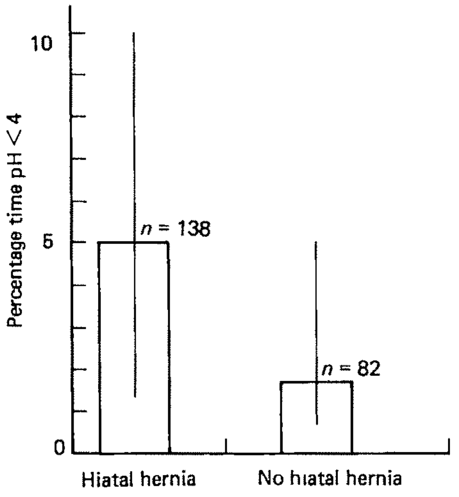

Figure 3 *Relation between presence of a hiatal hernia and percentage of time with pH < 4 by pH monitoring. Median and interquartile range Spearman rank correlation r = 0·33, P < 0·001*

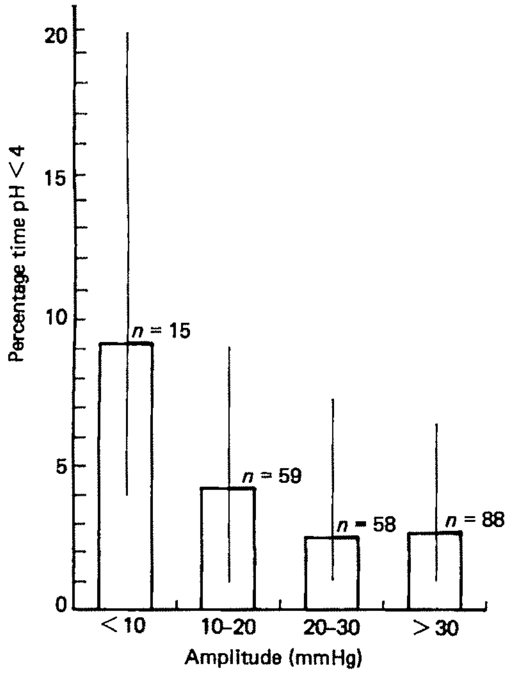

Figure 4 *Relation between amplitudes of the distal oesophageal contractions and percentage of time with pH < 4 by pH monitoring. Median and interquartile range Spearman rank correlation r = −0 18,* P *<0·01*

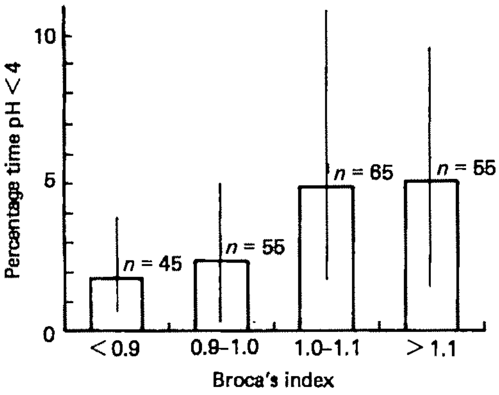

Figure 5 *Relation between Broca's index and percentage of time with pH < 4 at pH monitoring Median and interquartile range Spearman rank correlation r = 0 31,* P *< 0 001*

tence[15,16]. This was not seen in our study, probably because an overall length below 2 cm is an unusual phenomenon[16]

Another important component in the antireflux mechanism also seen in our study is the ability of the oesophagus to clear refluxed material[17], reflected by the amplitude of the peristaltic waves in the distal oesophagus[18]. The correlation between oesophageal emptying and acid exposure may, however, also be due to an effect of reflux on oesophageal motor function. The importance of this is supported by studies that have shown that medical and surgical treatment of reflux disease may restore oesophageal peristalsis[17,19]. It has also been suggested that a low pressure in the high pressure zone may be an effect of reflux rather than a cause[20]. Clinical studies have, however, shown that a hypotensive high pressure zone persists after healing of oesophagitis[21].

The presence of a hiatal hernia in our study significantly contributed to the amount of reflux in the multiple regression analysis Since the publication of the classic paper of Cohen and Harris[22] which showed that patients with and without oesophageal symptoms could be separated by the strength of the high pressure zone and not by the presence or absence of a hiatal hernia, attention has been focused away from a hiatal hernia as a pathogenic factor in gastro-oesophageal reflux disease. It has been proposed that a hiatal hernia may prevent reflux by reducing the gastric dilatation[23]. However, a correlation exists between the presence of a hiatal hernia and oesophagitis[24]. This could, at least partly, be due to the impaired clearance of the oesophagus in patients with a hiatal hernia[5],[25]. Furthermore, according to our study, a hiatal hernia influences reflux in some way other than by its influence on the pressure and intra-abdominal length of the distal oesophageal high pressure zone and on oesophageal peristalsis. The reason for this is unknown, but high intrahernial pressures may play a part[24] Other factors that have been previously thought to participate in the antireflux mechanism and that may be influenced by a hiatal hernia are the diaphragmatic pinchcock and the mucosal choke[26].

A weak but significant correlation was found between the age of the patients and the amount of reflux. The influence of age on reflux in normal subjects has been denied[27]. The increase in reflux with increasing age in reflux patients could be due to altered oesophageal motility in the elderly patient[28]

A correlation was also found between reflux and weight expressed as Broca's index. By multiple regression testing, however, Broca's index did not significantly improve the prediction of reflux. Increasing weight thus weakens the antireflux mechanism through the other determinants of gastro-oesophageal reflux.

Smoking did not affect the amount of gastro-oesophageal reflux in our study despite the clinical observations that smoking reduces the pressure in the high pressure zone and promotes reflux[29]. A plausible explanation for this may be that many patients with pathological reflux stop smoking, as smoking worsens their symptoms. Alcohol consumption was not a causative factor in reflux disease in our study but is an important differential diagnosis as alcohol may cause oesophagitis by directly irritating the oesophageal mucosa[30].

The pathophysiological mechanisms in reflux disease have been thoroughly discussed in the literature. The present study shows the relative importance of commonly discussed pathogenetic factors in a clinical population. The coefficient of determination derived from multiple regression analysis is an indication of the extent to which the variability in reflux can be explained by a factor or a combination of factors. *Table 1* shows that the pressure in the distal oesophageal high pressure zone is the single factor that best determines gastro-oesophageal competence and that it explains c. 17 per cent of the variability in acid reflux All the contributing factors in this study together explain 26 per cent of the variability in reflux. In other words, about three-quarters of the variability remains unexplained. There may well be other factors involved in gastro-oesophageal reflux that are not investigated in this study For instance, it

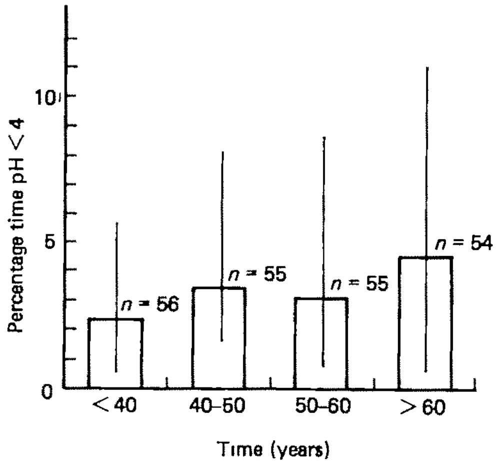

Figure 6 *Relation between age and percentage of time with pH < 4 at pH monitoring. Median and interquartile range. Spearman rank correlation r = 0·12,* P *<0·05*

has been postulated that gastric emptying is deranged in some reflux patients[31]. Acid hypersecretion[32], duodenogastric reflux[31-33] and eating and drinking habits have also been proposed as reflux promoting factors. It must also be remembered that we have only studied the high pressure zone during a short time span at oesophageal manometry while others have shown that the pressure of the high pressure zone may vary with time[34].

It is interesting to note that the three major components contributing to reflux in this study, a low pressure in the high pressure zone, hiatal hernia and a short intra-abdominal length, may be corrected by antireflux surgery At present there is no pharmacological agent available that has an enduring beneficial effect on these factors.

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Oesophageal transit of marshmallow after the Angelchik procedure

C. S. Robertson,
H. Smart,
S. S. Amar* and
D. L. Morris

Departments of Surgery and
**Radiology, University Hospital,*
Nottingham, NG7 2UH, UK
Correspondence to·
Mr D. L Morris

The oesophageal transit time of half a marshmallow was measured radiologically in 17 controls, 28 patients with gastro-oesophageal reflux pre-operatively, 36 patients soon after implantation of the Angelchik prosthesis (2–9 weeks) and in 23 patients later postoperatively (9–48 months). Sixteen postoperative patients also underwent oesophageal manometry. All control and pre-operative patients had a marshmallow transit time of less than 1 min; 67 per cent of the early postoperative patients had prolonged transit and 70 per cent of the late tests were similarly abnormal. Prolonged oesophageal transit as measured by marshmallow swallow correlated well with symptoms of solid food dysphagia. Most, but not all, patients with an abnormal marshmallow swallow had abnormal manometric findings. The oesophageal transit of solid food is significantly slowed after the Angelchik procedure and this is not a transient postoperative phenomenon.

Keywords: Oesophageal transit, Angelchik antireflux procedure

The Angelchik antireflux prosthesis is a horseshoe-shaped silicone elastomer shell filled with silcone gel. It has been extensively used in the treatment of gastro-oesophageal reflux. Clinical results[1] and objective assessment of reflux control[2,3] have been good. Dysphagia is the most common postoperative complication[3,4] and this can be separated into two distinct groups: the first is severe dysphagia, which is uncommon and in our experience is usually due to mechanical problems such as thoracic migration with angulation or the rotation/displacement phenomenon[5]; the second syndrome, which is seen much more frequently, is some difficulty in swallowing solids. Patients often report that certain foods, including bread and meat, 'stick' at the level of their lower sternum. This symptom usually settles spontaneously with time or after vomiting and only very rarely requires intervention—we have twice removed impacted food boluses endoscopically. Most patients learn to chew small amounts of their food well, not to rush their meals and to wash food down with fluid. These symptoms are usually tolerated by patients instead of their reflux pain and previous studies have claimed that this solid food dysphagia is only a transient phenomenon, usually settling within 3 months postoperatively[6].

We have investigated this symptom of solid food dysphagia by liquid barium swallows and have not found any abnormality. This paper describes our experience with the marshmallow barium swallow as a test of solid food oesophageal transit.

Patients and methods

Techniques of marshmallow and barium swallow

A standard liquid barium swallow was performed (100 ml E-Z barium*) and then the patient was asked to swallow half a marshmallow, (approximate diameter 20 mm) without chewing, followed by a further mouthful of barium All investigations were done by a single consultant radiologist (S S.A.). The examination was monitored by intermittent screening on an image intensifier and was recorded on video. The oesophageal transit time of the half marshmallow from the cricopharyngeus to entering the stomach was recorded. The radiographic appearance of the marshmallow is shown in *Figure 1*

Patients studied

A total of 40 patients, 24 of whom were male (median age 52 years), have undergone insertion of the Angelchik prosthesis, all had severe gastro-oesophageal reflux, unrelieved by adequate medical treatment, as documented by endoscopy/manometry and 24 h ambulatory pH monitoring None of the patients had a peptic oesophageal stricture or a primary oesophageal motility disorder pre-operatively.

Controls. Seventeen patients (eight men) with no evidence of oesophageal disease had a marshmallow swallow Their ages ranged from 29 to 70 years (median 48 years).

Pre-operative patients Twenty-eight patients underwent the marshmallow swallow procedure before insertion of the Angelchik prosthesis

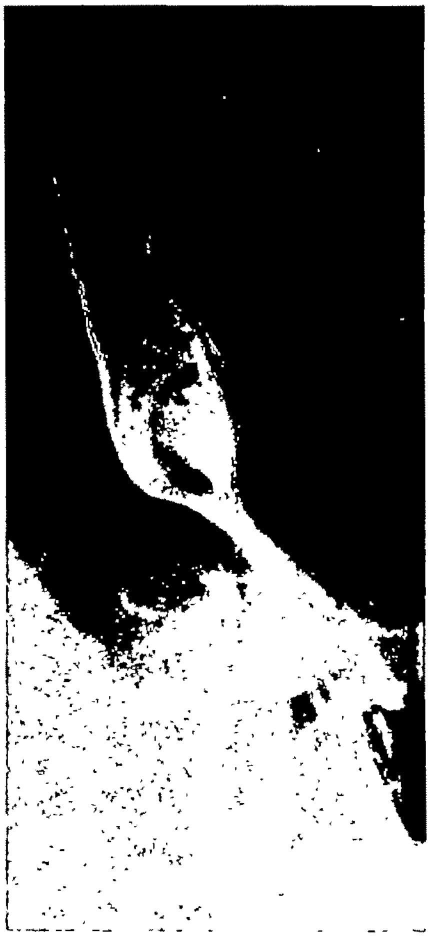

Figure 1 *Marshmallow in lower oesophagus lying just above the Angelchik prosthesis. The radio-opaque marker of the Angelchik prosthesis can be clearly seen*

E-Z barium was obtained from Henleys Medical Supplies, London, UK

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Post-Angelchik early. Thirty-six patients underwent the marshmallow swallow procedure soon after their operation (2–9 weeks). This included 17 patients who had a pre-operative marshmallow swallow

Post-Angelchik· late Twenty-three patients had a marshmallow swallow procedure performed 'late' at 9–48 (median 33) months after their Angelchik operation.

Manometry

Sixteen patients had oesophageal manometry after insertion of the Angelchik prosthesis Manometry was performed in fasted, supine patients with a triple-lumen polyvinyl catheter perfused at a constant rate (4 ml/h) with distilled water from a low compliance pneumohydraulic pump The catheter was connected to electrically isolated pressure transducers and recordings made onto a multichannel pen recorder. The station pull-through technique was used to identify the position and pressure of the lower oesophageal high-pressure zone. The response of this 'sphincter' to swallowing and oesophageal peristalsis was assessed by wet swallows with 5 ml water.

Results

Marshmallow transit time

Controls Of the 17 controls, all but 4 had an oesophageal transit time of <20 s and the remaining 4 all had transit times ⩽60 s (*Table 1*).

Pre-operative patients. Of the 28 patients investigated before the Angelchik procedure, 24 had a marshmallow transit time of <20 s and the remaining 4 had transit times ⩽60 s (*Table 1*).

Post-Angelchik: early. At the first postoperative marshmallow swallow, 24 of the 36 patients (67 per cent) had a transit time >60 s This included 17 patients who underwent marshmallow swallow both before and after insertion of the Angelchik prosthesis; the transit times are given in *Table 2.* All preoperative times were within the normal range but 10 of the 17 patients had a prolonged marshmallow transit time (> 1 min) postoperatively. The range of transit times was considerable, ten patients having a transit of ⩾3 min.

Post-Angelchik: late. A total of 23 patients underwent a late postoperative marshmallow swallow and in 16 patients (70 per cent) transit was prolonged (> 1 min) (*Table 1*) All of these patients had undergone an early postoperative marshmallow swallow and a comparison of their early/late transit times is shown in *Figure 2.* Of the 16 patients with a prolonged (> 1 min) transit time in the early postoperative period, 3 showed a significant improvement later but only 2 returned into the normal range and 9 patients had slower transit at their later postoperative marshmallow swallow than at their early postoperative investigation. The median marshmallow transit time was 3·5 min in the early postoperative period and 3·8 min in the late postoperative (*P* = n.s.). Of the seven patients with a normal early marshmallow swallow time, two were abnormal at the second investigation.

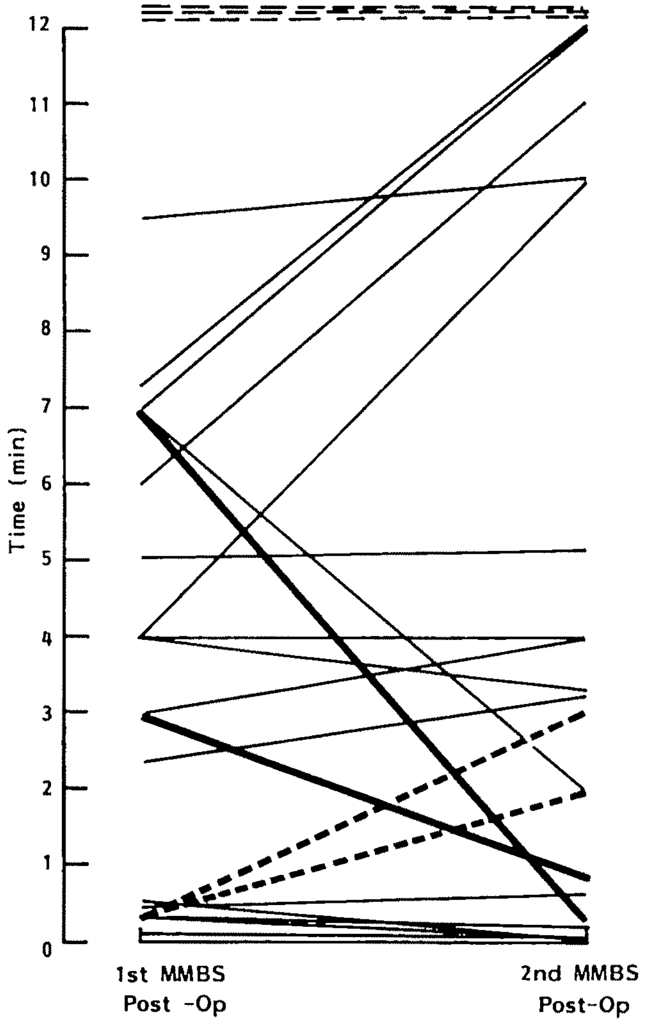

Figure 2 *Marshmallow oesophageal transit times (MMBS) early and late after insertion of the Angelchik antireflux prosthesis:* ——, *2 patients in whom the transit time was prolonged at the first examination but returned to normal with time,* – – –, *2 patients in whom the transit time was initially normal but was prolonged at later examination,* — — —, *3 patients with transit times >12 min;* ——, *the majority of patients (those who had normal transit times continued to do so while those with early abnormalities retained prolonged transit times)*

Table 1 *Transit time for marshmallow*

	No of subjects	Marshmallow transit time (s)		
		<20	20–60	>60
Controls	17	13	4	0
Pre-operative patients	28	24	4	0
Post-Angelchik				
Early	36	7	5	24 (67%)
Late	23	5	2	16 (70%)

Table 2 *Transit time for marshmallow for the same 17 patients before operation and early postoperatively after insertion of the Angelchik prosthesis*

	No. of subjects	Marshmallow transit time (s)		
		<20	20–60	>60
Pre-operative patients	17	15	2	0
Post-Angelchik· early	17	7	0	10

Correlation of symptoms and marshmallow transit time

Thirty-eight patients complained of some dysphagia for solids after the Angelchik procedure and all of these had a prolonged marshmallow transit time at some time postoperatively In addition, three patients had severe dysphagia due to the rotation/displacement phenomenon[5]; the prosthesis had to be removed in all cases. Only two patients never complained of dysphagia and both had normal marshmallow transit times.

Correlation of manometry and marshmallow transit time

Of the 16 post-Angelchik patients studied by oesophageal manometry, 7 had abnormal oesophageal motility characterized by a non-relaxing lower oesophageal high-pressure zone in 5, an absence of co-ordinated peristalsis in 1 and repetitive peristaltic activity in 1. Of these 16 patients, 10 had a prolonged marshmallow transit time and all 7 patients with a manometric abnormality were identified by marshmallow swallow.

Discussion

The Angelchik prosthesis is widely used in the surgical management of gastro-oesophageal reflux. We have previously reported a high incidence of dysphagia for solid food[3] after its use. This problem has not previously been investigated by the novel technique of marshmallow swallow. There are several advantages to this technique: it is inexpensive and can be performed in any hospital; it allows a liquid examination to be done to exclude structural/displacement problems; the marshmallow floats on top of the barium and allows an assessment of oesophageal peristalsis; and, finally, if the marshmallow becomes impacted in the oesophagus it will slowly dissolve (*c.* 30 min) as it is composed almost entirely of sugar, thus avoiding troublesome bolus obstruction. Although the technique does involve radiation exposure this is limited by the intermittent screening technique. We have shown that oesophageal transit of this bolus is accomplished in $\leqslant 1$ min in controls without any evidence of oesophageal disease and, more importantly, that patients with reflux also have normal oesophageal transit. Previous authors[7,8] report a total of 20 control patients all with a transit time of <1 min using a radionuclide marshmallow technique. We would not argue that all patients with reflux have entirely normal transit—motor abnormalities may well occur secondary to oesophagitis and stricture could clearly interfere with transit—but our group of reflux patients had normal transit pre-operatively. When the same patients were examined after insertion of the Angelchik prosthesis the majority had delayed transit. In all cases the half marshmallow was arrested at the cardia just proximal to the Angelchik prosthesis

We have also demonstrated objectively that this is not a transient postoperative phenomenon in that, of a group of patients who underwent marshmallow swallow a median of 33 months after operation, 70 per cent had prolonged transit. There was a trend to slower transit at the late postoperative marshmallow swallow and more patients had worse rather than improved transit.

The reason for delayed transit of solids following insertion of the Angelchik prosthesis is not clear. The operation certainly gives good control of gastro-oesophageal reflux[3] and none of our patients had a peptic stricture before operation and none developed a peptic stricture postoperatively. Oesophageal manometry postoperatively revealed five patients with a non-relaxing high-pressure zone and all the marshmallows were arrested just proximal to the Angelchik. Symptoms have persisted postoperatively and these factors suggest that dysphagia may be a direct mechanical effect, perhaps due to posterior buttressing of the oesophagus.

Practical advice must be given to patients to encourage them to chew their food thoroughly, to avoid rushing meals and to avoid potentially ulcerogenic tablets, which might well be retained in the lower oesophagus, in favour of liquid formulations.

The Angelchik procedure clearly slows the transit of solid food through the oesophagus and this effect is perhaps permanent. The effects of comparable surgical procedures have not been reported but we are currently evaluating patients randomized to either the Angelchik or Nissen operations.

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Liver transplantation for primary and secondary hepatic apudomas

J. C. Arnold, J. G. O'Grady, G. L. Bird, R. Y. Calne* and R. Williams

*Liver Unit, King's College Hospital and School of Medicine and Dentistry, London and *Department of Surgery, Addenbrooke's Hospital, Cambridge, UK*

Correspondence to.
Dr R. Williams, Liver Unit, King's College Hospital, Denmark Hill, London SE5 9RS, UK

Four patients underwent liver transplantation in the Cambridge/King's College Hospital programme for malignant primary and secondary apudomas, secreting various peptide hormones and uncontrollable by standard treatment techniques. After transplantation all patients had excellent symptomatic relief and specific peptide hormone levels fell to normal ranges. Two patients remain alive and well after 38 and 22 months, the latter with recurrence of slight tumour-related symptoms and elevation of the specific secretory product. The other two patients died from chronic graft rejection 7 and 8 months after transplantation.

Keywords: Liver transplantation, apudomas, carcinoid syndrome, peptide hormone producing tumours

Current therapy for malignant apudomas including resection, embolization or chemotherapy, as well as pharmacological blocking agents, may give good palliation for a prolonged period both in the primary tumour arising in the liver and hepatic metastatic disease[1–3]. However in cases where such measures are no longer effective and in certain instances where tumour is confined to the liver, transplantation may provide both long-term symptomatic relief and sometimes cure.

In the present report we describe the outcome of four patients transplanted for primary and secondary apudomas, who had distressing and uncontrollable symptoms related to hormone production. The effect of the procedure on the different secretory products is also reported.

Case reports

Case 1

A 35-year-old woman had been aware of a mass in her upper abdomen for more than 10 years before the diagnosis of a massive neuroendocrine type liver tumour was established in 1981 on histological and electron microscopical features Considerably elevated levels of pancreatic polypeptide (>1000 pmol/l, normal <300 pmol/l), gastrin (81 pmol/l, normal <40 pmol/l) as well as urinary vanillinmandelic acid (VMA) (920 μmol/24 h, normal 12–44 μmol/24 h) were detected. In the 4 years following the diagnosis, she experienced increasing lethargy, abdominal discomfort, profuse sweating and weight loss On reinvestigation, in 1985, no extrahepatic tumour spread was found on computed tomography (CT) and bone scans or on staging laparotomy

At transplantation, performed in March 1985, large tumour masses involving both lobes were seen in a 5 7 kg liver, and a tiny tumour deposit, which was found in one hilar lymph node, was removed. Postoperatively peptide hormone levels fell to within the normal range and 38 months post-transplantation she remains well without any signs of recurrence.

Case 2

In 1983, a 47-year-old man was found, on the evidence of an enlarged liver but without any related symptoms, to have an apudoma, he had highly elevated bood levels of somatostatin (>2000 pmol/l, normal <100 pmol/l) and glucagon (84 pmol/l, normal <50 pmol/l) Despite five courses of treatment of Adriamycin® (Farmitalia Carlo Erba, St Albans, UK) and fluorouracil he subsequently developed diarrhoea and hyperglycaemia with intermittent hypoglycaemic attacks, unrelated to insulin treatment in 1984 Additional treatment with mitomycin and antiandrogens also failed to produce a symptomatic response Further investigations with hepatic arteriography revealed an avascular tumour and no extrahepatic tumour spread was found on CT scan

Liver transplantation was performed in August 1985. Histology and electron microscopy confirmed the diagnosis of an apudoma in the resected liver (3 7 kg in weight). The tumour involved both lobes with similar lesions in a small nodule in the body of the pancreas and in enlarged abdominal lymph nodes which had also been resected Post-transplantation the tumour-specific symptoms were relieved immediately and the peptide hormone levels fell to within the normal range. Some 4 weeks postoperatively he developed primary cytomegalovirus infection and 11 weeks later chronic rejection (vanishing bile duct syndrome) was diagnosed on liver histology. His general condition remained good for a further 3 months. Follow-up CT scans showed no tumour recurrence and peptide hormone levels were still within the normal range shortly before his death from chronic rejection in March 1986.

Case 3

A 49-year-old man had an 8-year history of severe diarrhoea and flushing attacks Resection of a carcinoid tumour arising in the small intestine and ligation of two supplying arteries for multiple metastases throughout the liver was performed in 1984. Postoperatively, four courses of cytotoxic therapy with streptozocin and fluorouracil were given as well as continuous treatment with the antiserotonin agents methysergide and cyproheptadine, with only slight symptomatic relief. Although the highly elevated urinary 5-hydroxyindoleacetic acid (5-HIAA) was reduced from 1385 to 390 μmol/24 h (normal range 15–75 μmol/24 h) he started having episodes of severe bronchospasm in 1985 Because of the symptomatic deterioration and impossibility of arterial embolization, liver transplantation was carried out in July 1986.

The resected liver weighed 5 4 kg with both lobes largely occupied by tumour and with tumour involvement of the falciform ligament as well as hilar lymph nodes. All symptoms of the carcinoid syndrome resolved completely after transplantation and the urinary 5-HIAA levels fell to within the normal range After 10 months significantly elevated levels (219 μmol/24 h) were detected again (*Figure 1*) and 17 months after transplantation he began to have occasional diarrhoea. Assessment 20 months post-transplantation found him feeling well without flushing or bronchospasm No tumour recurrence could be detected radiologically or on abdominal ultrasound.

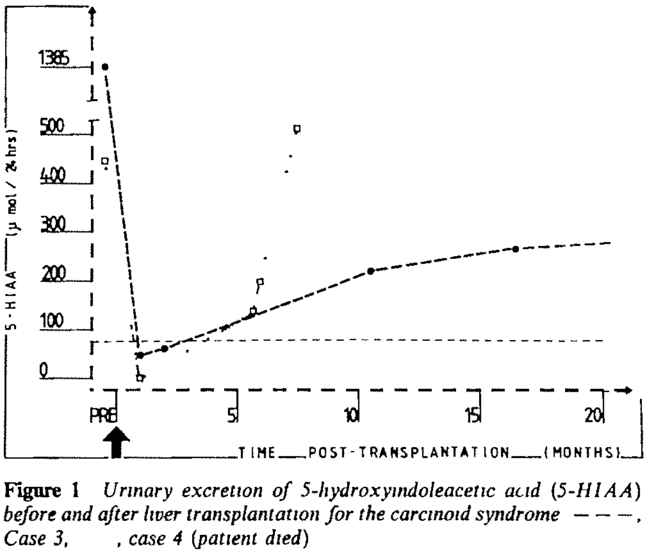

Figure 1 *Urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) before and after liver transplantation for the carcinoid syndrome — — —, Case 3, , case 4 (patient died)*

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Case 4

A 53-year-old woman presented in September 1985 with severe diarrhoea, nausea, vomiting and intermittent flushing attacks 40 months after resection of a lung carcinoid tumour. Her liver was found to be grossly enlarged with metastases in both lobes. Hepatic artery embolization was performed on two occasions with good symptomatic relief, high urinary 5-HIAA secretion levels (586 and 407 μmol/24 h, respectively) became undetectable after each treatment for up to 6 months. There was further symptomatic deterioration with distressing diarrhoea, weight loss and massive abdominal distension and an isotope bone scan revealed small tumour deposits in the lumbar spine

Liver transplantation was performed in November 1986. The resected liver weighed 5·6 kg with tumour deposits in both lobes and large hilar lymph nodes. No further abdominal tumour spread was seen She was discharged from hospital after 3 weeks completely free of carcinoid-related symptoms. Subsequently, she had complications relating to the biliary tract anastomosis with cholangitis and after 4 months signs of chronic rejection (vanishing bile duct syndrome) were apparent. The urinary 5-HIAA secretion levels, initially negative, started to rise again 6 months after transplantation (*Figure 1*) but she remained free of carcinoid-related symptoms. Her general condition deteriorated and she died from chronic graft failure complicated by pulmonary infection in July 1987.

Discussion

The indication for transplantation in these four patients was the presence of distressing symptoms in association with excessive peptide hormone secretion, together with massive liver enlargement. In three out of four cases currently accepted methods of treatment[1–3] such as ligation and embolization of the hepatic artery, various combinations of chemotherapy and pharmacological blocking agents could not be repeated or were no longer effective. Both patients with hepatic metastases from carcinoid tumour had had the primary lesions removed previously from the lung and small intestine, respectively. The origin of the mainly pancreatic polypeptide producing tumour in case 1 was likely to have been bile duct epithelium as described previously[4]. The main tumour mass of the somatostatinoma in case 2 was in the liver, but it is possible that the single small tumour node in the body of the pancreas identified and removed during the transplantation was the primary tumour.

All patients had excellent relief of hormone-related symptoms and symptoms related to the massively enlarged liver. Specific peptide hormone levels fell to within the normal range in each patient and two of the patients continue to do well and are alive 38 and 22 months after transplantation. Unfortunately the other two patients developed chronic graft rejection preceded by cytomegalovirus and biliary tract obstruction with cholangitis respectively, and it was these complications and not tumour recurrence which led to their deaths.

Complete symptomatic remission of the carcinoid syndrome was achieved up to 17 months post-transplantation in one patient and to the time of death in the other. Urinary 5-HIAA levels have not been significantly elevated for 6 and 10 months, respectively (*Figure 1*). Liver transplantation for hepatic metastases of different primaries other than apudoma showed poor results in the initial series in the Cambridge/King's College Hospital programme[5]. Only three out of six patients survived more than 3 months and these died between 22 and 41 weeks from recurrent disease. Pichlmayr's group also reported a short period of survival[6]. More encouraging data come from the Vienna group with an estimated 1-year survival of 70 per cent and one patient tumour-free at 3 years; nine patients dealt with had hepatic metastases from radically resected primary colon carcinoma (not exceeding Dukes' C_1) and from a phaeochromocytoma in one case[7]. Of the four patients transplanted for secondary heptic apudomas by Iwatsuki *et al.*[8], three are alive and tumour-free after 2–21 months, while the remaining patient died from perioperative complications.

To date the recurrence rate of primary hepatocellular carcinoma with symptomatic presentation is 64·9 per cent, with 1- and 2-year survival rates of 45 and 38 per cent respectively[5], and it is 77·8 per cent in the Pittsburgh programme[9]. Central and peripheral cholangiocarcinomas have an even worse prognosis with 1-year survival rates of 30·7 and 38·4 per cent respectively. The two patients with primary apudomas thought to be arising in the liver remained free of tumour clinically and radiologically and there was no evidence of elevated peptide hormone levels after 38 months and at the time of death 7 months post-transplantation. Compared with other types of hepatic malignancy, apudomas with their longer history and often lower intrinsic malignancy may represent a relatively favourable group with respect to transplantation.

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Cholecystectomy and colorectal cancer

R. J. Moorehead and S. T. D. McKelvey

Department of Surgery, Queen's University of Belfast, Belfast, UK

Correspondence to.
Mr R. J Moorehead, University Department of Surgery, Queen Mary Hospital, Pokfulam Road,
Hong Kong

This review examines the evidence for and against an association between cholecystectomy and colorectal cancer.

Keywords: Cholecystectomy, bile acids, colorectal cancer

There is a considerable amount of epidemiological evidence suggesting that bile acids are aetiologically important in the development of colorectal cancer[1]. While several clinical studies have demonstrated abnormalities in bile acids of those with adenomas and carcinomas of the large bowel[2–4], the precise action of bile acids in tumour promotion or initiation remains to be determined

Certain surgical procedures can affect the size of the bile acid pool with consequent changes in the proportions of bile acids present in duodenal bile Cholecystectomy is one such procedure. It is now generally accepted that the size of the bile acid pool negatively correlates with the level of deoxycholic acid present in bile, i.e. a smaller pool is associated with a greater proportion of deoxycholic acid[5]. While some may argue that it is the presence of gallstones that produces this change in bile acid metabolism[6] it is generally agreed that cholecystectomy patients have a significantly increased proportion of secondary bile acids in bile, chiefly deoxycholic acid[7–10]. As a possible explanation for these changes it is suggested that, while before cholecystectomy the bile acid pool circulates two or three times per meal, after cholecystectomy the pool circulates even during the fasting state. This enhanced circulation results in an increased exposure of bile acids to the degrading action of intestinal bacteria. As a result there is an increased input of secondary bile acids from the intestine into hepatic bile with a corresponding reduction in primary bile acid synthesis owing to increased feedback inhibition[8,9].

Such observations on the effects of cholecystectomy on bile acid metabolism, together with epidemiological, clinical and experimental evidence[11] suggesting possible carcinogenic or co-carcinogenic properties of bile acids have led to increased speculation on the hypothesis that patients with a history of cholecystectomy may have an increased risk of developing colorectal cancer.

While confirmation of such a link would give further weight to the argument which links bile acids with bowel cancer, it would also be of some clinical significance by clearly identifying an at-risk group. There have been several studies investigating the possibility of a link between cholecystectomy and large bowel cancer. The findings of these studies have been varied and in some cases contradictory. In many instances differences in methodology and inadequacy of study group size may account for these variations

The argument for and against an association

There have been many studies suggesting the existence of an association between bowel cancer and cholecystectomy[12–21]. Undoubtedly the best of these is the prospective study by Linos *et al.*[14] who followed up 1681 post-cholecystectomy patients and demonstrated an increased relative risk of developing colorectal cancer of 1·7. They also reported an even more marked risk of 2·1 for the development of right-sided lesions in women (*Table 1*). Unfortunately not all of the other studies go as far as reporting relative risks but those that do claim increased incidences for colonic cancer of between 1·59 and 2·27[15,16] Even higher relative risks of up to 3·5 have been reported for right-sided cancer in women[20], with the highest so far being 4·5 for sigmoid lesions[18], though neither of these studies demonstrated anything more than a trend for an overall increased risk. Caution is required in accepting these increased risks at face value as some of the studies from which they are derived may be flawed through selection of cases and controls In our own study[20] and those from Regula *et al.*[18] and Turnbull *et al.*[16] controls were all drawn from a hospital population It could be argued that such a group is not representative of the general population. Similarly, in the study by Turunen and Kivilaakso[15] both cancer patients and controls were drawn from those undergoing post-mortem examination with the obvious selection bias that this might entail.

Others have divided their cancer patients into cholecystectomy and non-cholecystectomy groups and compared tumour distribution between the two without reference to outside controls[12,13,19]. While this may give information on any potential predisposition for tumour sites in cholecystectomy patients it does not give information on the overall risk compared with the rest of the population. A major criticism levelled against most of these investigations is that they are retrospective case control studies. The finding of an association between two conditions in this type of study could well be due to chance producing a Berksonian bias in the result[14,22]. Therefore one investigation alone suggesting an association between cholecystectomy and colonic cancer might be of interest yet not really significant. That several have observed an association between the two conditions suggests that the result may not be due to chance. Further, the reported increased risk of proximal colonic tumours in some of these studies[12–15,20], suggests that the link between the two conditions may indeed be a causal one. This predilection for right-sided tumours in some studies may be explained by proposing that higher levels of these bacterially modified bile acids are absorbed more proximally in the colon. That some have noticed this finding in women only may be a reflection of the increased incidence of cholecystectomy in women compared with men.

There are more recent reports giving further support to the association. In a colonoscopic study, patients over 60 years of age with more than 10 years having elapsed since their cholecystectomy were found to have an increased incidence of both adenomas and carcinomas of the colon when compared with controls known to have asymptomatic gallstones[17]. A further similar study reported an increased incidence of adenomas in post-cholecystectomy women with a trend for a preponderance of proximal tumours[21].

The evidence against an association between colorectal cancer and previous cholecystectomy[23–33] is open to criticisms similar to those that applied to the studies reporting an

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Table 1 *Studies that have investigated the possibility of an association between cholecystectomy and colorectal cancer*

Reference	Number of cases	Type of cases	Relative risk	95% Confidence interval	*P*	Tumour site (if applicable)
Vernick *et al* [12]	706	Cancer	2·23	(1·33–3·75)	*	Right colon
Vernick and Kuller[13]	150 150	Right colon cancer Left colon cancer	1·87	(0·89–3·91)	*	Right colon
Linos *et al.*[14]	1681	Cholecystectomy	1·7 2·1	(1·1–2·5) (1·1–3·6)	* *	All sites Right colon, women
Turunen and Kivilaakso[15]	304	Post-mortem cancer	1·59 3·0	* *	<0·05	All sites Right colon
Turnbull *et al* [16]	305	Cancer	2·27	*	<0·01	All sites, women
Mannes *et al* [17]	331	Cholecystectomy	*	*	<0·05	All sites
Regula *et al* [18]	200	Cancer	4·5	*	<0·05	Sigmoid colon, women
Giordano and Di Bella[19]	177	Cancer	*	*	*	All sites
Moorehead *et al* [20]	598	Cancer	3·5	(1·7–7·5)	<0·005	Right colon, women
Llamas *et al* [21]	72	Adenoma	*	(1·7–*)	<0·01	Right colon, women (trend)
Hoare[23]	100	Cancer	*	*	*	—
Weiss *et al* [24]	141	Cancer	1·4	(0·8–2·5)	*	—
Abrams *et al* [25]	249 582	Cholecystectomy Cancer	* *	* *	* *	— —
Vobecky *et al* [26]	207	Cancer	*	*	*	—
Adami *et al* [27]	16773	Cholecystectomy	0·85	(0·68–1·07)	*	—
Blanco *et al.*[28]	*	*	1·2	(0·6–2·2)	*	—
Eriksson and Lindstrom[29]	1061	Post-mortem cancer	*	*	*	—
Preitner *et al* [30]	237 194	Cancer Post-mortem cancer	*	*	*	—
Simi *et al.*[31]	250 200	Cancer Cholecystectomy	*	*	*	—
Spitz *et al* [32]	267 268	Right colon cancer Left colon cancer	1·49	(0·83–2·67)	*	—
Machnik *et al* [33]	449	Post-mortem cancer	*	*	*	—

* Not specified

association. Hoare's conclusions cannot be accepted as they came from a small retrospective case control study of only 100 patients[23]. One would not expect significant differences from a study of this size unless the incidence of cholecystectomy in cancer patients compared with controls was very high (*Table 1*). Similarly, although Weiss *et al.*[24] set out to study 243 cancer patients data were only obtained from 141. The authors accept that uncertainty surrounded their results because of the small number of patients studied. From their reported relative risk and confidence intervals one could speculate that had they studied a larger number of patients then evidence to support an association may have been demonstrated.

The investigation by Eriksson and Lindstrom[29], although large (1061 cases), involved cases and controls coming to hospital post mortem Such groups might be considered unrepresentative of the general population. The same criticism could be applied to the smaller studies by Preitner *et al.*[30] and Machnik *et al.*[33]. The case control studies by Vobecky *et al.*[26], Preitner *et al.*[30], Simi *et al* [31] and Spitz *et al.*[32] are similar to the case control studies cited in favour of an association. The same shortcomings of this type of study therefore apply but perhaps more so in view of the comparatively small numbers included in each. In a second part of their study Simi *et al.*[31] made an attempt to follow up 200 post-cholecystectomy patients. Unfortunately endoscopic or X-ray examinations were performed in only a few. Their results are therefore of limited value.

Abrams *et al.*[25] did investigate a large number of both cholecystectomy and cancer cases. However, no matched controls were used thereby casting doubts over the validity of any conclusions. In the population study by Blanco *et al.*[28] the precise number of patients who replied to the questionnaires is not stated. It is therefore difficult to make any comment on their findings.

Of all the papers finding no evidence of an association between colorectal cancer and cholecystectomy, there is only one that stands out[27] In an impressive follow-up of 16773 cholecystectomy cases by Adami *et al.*, no increased risk of large bowel cancer was observed. Clearly, findings such as this cannot be simply dismissed.

Discussion

The precise relationship between cholecystectomy and the development of large bowel cancer remains controversial. The conflicting results from the studies already outlined have done little to settle this important issue. Perhaps much of the conflict is artificial as many of the studies have serious limitations in design, size and make-up of subject groups and controls. Of those studies not demonstrating an association between cholecystectomy and bowel cancer, only that from Adami *et al* [27] stands up to criticism. However, a geographical factor may have to be considered with their results. The incidence of colon and rectal cancer in Sweden has been reported as 16 and 12·8 per 100000 respectively[34]. In Northern Ireland, where an association between cholecystectomy and large bowel cancer has been demonstrated, the incidence of colon and rectal cancer is considerably higher at 21·9 and 18·7 per 100000 respectively. This regional variation in the incidence of colorectal cancer may be an important factor to be taken into account when comparing the different results from Sweden and Northern Ireland This does not necessarily reduce the case against an association as much of the evidence for an association is derived from unsatisfactory studies However, as was the case with the study of Adami *et al.*[27], the findings of the prospective study by Linos *et al.*[14] cannot be simply dismissed. Indeed, the reported increased incidence of right-sided colonic cancer in post-cholecystectomy women from some of the retrospective studies adds weight to their conclusions

In most of the papers mentioned, the selection of suitable controls has been a major problem. Theoretically post-cholecystectomy cases should be compared with age- and sex-matched controls known to have asymptomatic cholelithiasis. The task of obtaining such a group from the general population would be virtually impossible Most authors have therefore had to compromise and use the best available group of controls. It is possible that most of these controls did not have biliary tract disease. As a result the comparison that has been made in many of the papers does not address the effect of cholecystectomy as such but the effect of symptomatic gallstones requiring cholecystectomy *versus* disease-free controls.

The only paper that has managed to make a direct comparison between cholecystectomy cases and those with asymptomatic gallstones is that by Mannes *et al.*[17]. Although they found an increased risk of adenomas and carcinomas in cholecystectomy cases, their study was biased in that all cases and controls were undergoing investigative colonoscopy

If one thing is clear it is that further retrospective studies will not clarify this important issue. The question will only be finally resolved by prospective studies following up post-cholecystectomy patients, with colonoscopy or barium enema, to determine whether the incidence of tumours is really increased We have begun such a study based on the observations of Mannes *et al.*[17]. In an attempt to maximize the yield from screening cholecystectomy patients we are following up those over 60 years of age with 10 years or more having elapsed since surgery with double contrast barium enemas and sigmoidoscopy The selection of controls for this study has proved to be a major problem as it was impracticable to submit a control group to the same investigations. A compromise had to be made and post-mortem patients were used. In an attempt to try to reduce any hospital bias an equal number of cases undergoing non-hospital post mortems were used. Obviously this is an area for potential criticism but nevertheless our preliminary results have shown a fourfold increase in the incidence of adenomas and carcinomas following cholecystectomy[35].

Some groups have reported an increased incidence of large bowel cancer in those with a history of cholelithiasis rather than cholecystectomy[36,37]. However, even if an association between colorectal cancer and biliary tract disease were supported by all, it is possible that there is no direct link between either cholecystectomy or cholelithiasis and large bowel cancer. It may be that the appearance of an association in some reports is because those whose diet predisposed to one disease may well have increased their risk of developing the other. Whether this possible relationship is directly causal or not, those with a history of previous cholecystectomy are readily identifiable. Epidemiologists might suggest that such a group could be worth screening for both colorectal adenomas and carcinomas. However, even if the evidence supporting an association with colorectal cancer were universally supported in absolute terms, cholecystectomy patients may not constitute such a high-risk group to necessitate screening. The reported overall risks of between 1·59 and 2·27 would support this contention.

If such a screening programme were carried out it would have two obvious benefits: first, it would give valuable information on the pathogenesis of large bowel cancer and, secondly, it would determine conclusively whether there is a relationship between cholecystectomy and the subsequent development of colorectal tumours.

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Alcohol sclerotherapy of non-parasitic cysts of the liver

R. Andersson,
B. Jeppsson,
A. Lunderquist* and
S. Bengmark

Departments of Surgery and
**Roentgenology, Lund University,*
S-221 85 Lund, Sweden
Correspondence to:
Dr R. Andersson

Between 1980 and 1987, nine patients with non-parasitic cysts of the liver were treated with computed tomography-guided percutaneous puncture and evacuation of the cyst contents followed by injection of absolute alcohol as a sclerosing agent. During the same period only one patient was treated with surgery. The patients included seven women and two men with a mean age of 62 years. Three patients had a single cyst and six patients had multiple cysts. The size of the largest cysts varied between 5 and 20 cm (mean 10 cm). Patients with multiple liver cysts had repeated punctures and sclerosing procedures (up to eight times); 50–3100 ml of cyst fluid (mean 650 ml) was drained per procedure. One patient had symptoms of moderate alcohol intoxication; otherwise no complications were noted. Follow-up was performed with computed tomography or ultrasonography for 8–54 months (median 18 months). The results have been considered successful in eight out of nine patients who had cyst regression and reduced symptons. Two patients, however, required additional surgical treatment due to residual and multiple cysts. Computed tomography-guided alcohol sclerotherapy of non-parasitic liver cysts appears to be a safe and effective initial therapy.

Keywords: Liver cysts, non-parasitic, computed tomography, percutaneous aspiration, alcohol sclerotherapy

Non-parasitic liver cysts are either congenital or acquired Congenital cysts are more common and considered to be embryological malformations[1,2]. They can occur as single or multiple cysts with a varying size. There is a female preponderance and symptoms, if they occur, usually first appear in adulthood[3]. The symptoms have mainly been attributed to hepatomegaly, increased pressure within the cyst or pressure on the surrounding organs. Signs of impaired liver function such as jaundice are less frequent[1,4,5]. Most congenital cysts, however, are asymptomatic and require no treatment[1,6]. In a large series of 88 000 laparotomies, 82 solitary liver cysts were found[1] and of these only approximately one-sixth were considered to have caused symptoms

Conservative treatment with aspiration of cyst fluid alone has been associated with a high recurrence rate[6]. Surgical treatment has thus been advocated for all forms of symptomatic liver cysts[1,6].

We wanted to test whether cyst recurrence could be avoided after percutaneous aspiration followed by the instillation of a sclerosing agent In this study we describe a series of patients with non-parasitic liver cysts treated initially with computed tomography-guided percutaneous puncture, decompression and sclerotherapy with absolute alcohol.

Patients and methods

Between 1980 and 1987, nine patients with non-parasitic cysts of the liver were treated with puncture, drainage and injection of absolute alcohol During this period only one patient, with a single cyst not considered accessible for percutaneous puncture, was successfully managed with a surgical fenestration procedure. The patients treated with alcohol sclerotherapy consisted of seven women and two men with a mean age of 62 years (range 40–77 years) Three patients had a single cyst and six had multiple cysts. In seven patients, cysts were limited to the right lobe, while two patients with multiple cysts also had left lobe involvement In three cases a concomitant polycystic renal disease was diagnosed One patient had a post-traumatic liver cyst, while the other patients were considered to have congenital liver cysts The aetiology and localization of the liver cysts are summarized in *Table 1* All patients had symptoms· abdominal pain in eight, a palpable mass in seven and weight loss in one Diagnosis was reached by ultrasonography in seven patients, computed tomography in one and peroperatively (during a renal operation) in one patient. The size of the largest cysts varied between 5 and 20 cm (mean 10 cm) in diameter.

Before the start of therapy the presence of parasitic disease or malignancy was excluded. Under guidance of computed tomography the main liver cyst was punctured with a 5Fr polyethylene catheter sheathed needle The sheath was supplied with several sideholes at the tip to facilitate aspiration of fluid With the aid of a guide-wire the catheter was coiled within the cyst, reducing the risk of displacement when the cyst was evacuated and collapsed. After cyst fluid aspiration, 20–100 ml absolute alcohol (95 per cent) was instilled and as much as possible was reaspirated from the cyst after 10–20 min Liver function tests were performed before as well as 1, 4 and 24 h after alcohol injection Serum ethanol levels were also analysed after the administration of alcohol

Results

Some patients noted slight abdominal pain following ethanol instillation, but otherwise the procedure was well tolerated. One elderly woman had symptoms of moderate alcohol intoxication; her serum ethanol was 8·7 mmol/l, 4 h after alcohol injection. No other complications were noted. Patients with multiple liver cysts had repeated punctures and alcohol instillations at intervals up to eight times before the cyst disappeared. A total of 29 punctures and injections were performed (3·2 procedures per patient) A mean of 650 ml fluid was drained per puncture with a range of 50–3100 ml. The amounts drained gradually diminished with a mean of 1230 ml drained at the first puncture, 540 ml at the second, and 320 ml at the third. Liver function tests were unaffected by the treatment. The patients were followed with computed tomography or ultrasonography for a median of 18 months (range 8–54 months) after treatment. The results were considered good or excellent (*Figure 1*) in eight of the nine

Table 1 *Aetiology, number of cysts and localization of liver cysts*

	No of patients ($n=9$)
Congenital	8
Polycystic disease	3
Post-traumatic	1
Multiple cysts	6
Single cysts	3
Right liver lobe	7
Right + left liver lobe	2

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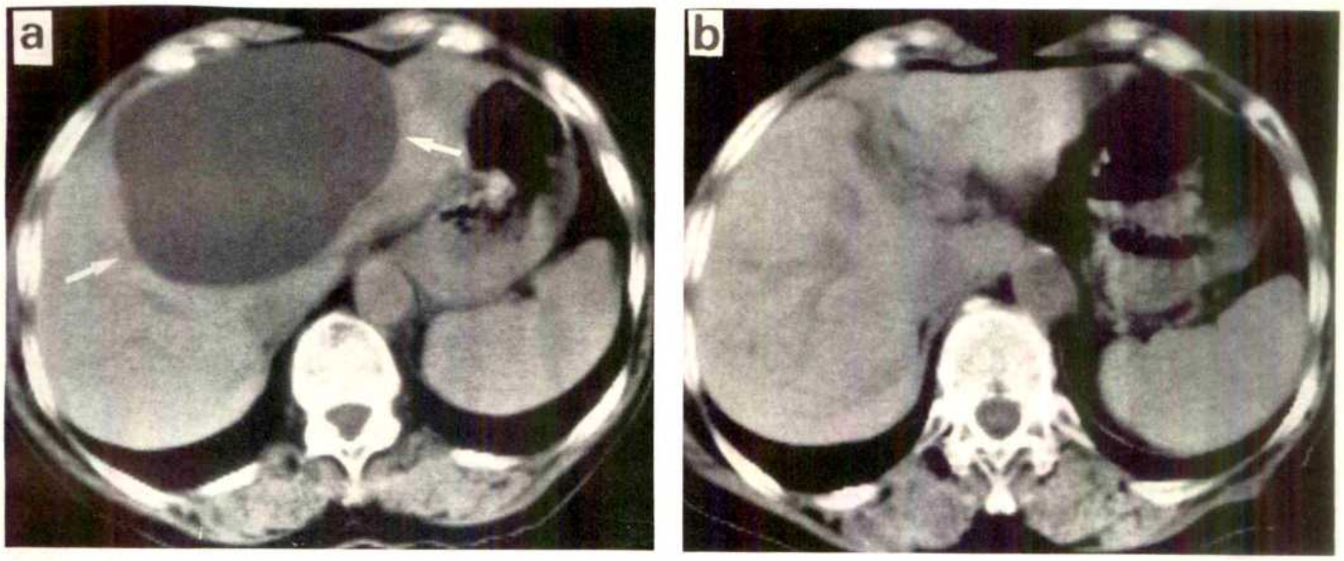

Figure 1 **a** *Computed tomography scan of the liver of a 74-year old woman with a large benign hepatic cyst. The cyst was aspirated and sclerosed with absolute alcohol;* **b** *a scan of the same region of the liver 3 months later shows complete disappearance of the cyst*

Table 2 *Results of repeated puncture and alcohol instillation in patients with non-parasitic liver cysts*

Patient	Age (Years)	Sex	No. punctures	Follow-up (months)	Results after treatment	
					Symptoms	CT/ultrasound
1	77	F	4	52	None	Regression*
2	40	F	2	18	Unchanged	Unchanged
3	50	F	8	14	Diminished	Regression*
4	62	F	4	13	Diminished	Regression*
5	62	M	2	54	None	Regression*
6	74	F	1	8	None	Regression*
7	74	F	2	9	None	Regression*
8	59	F	4	31	None	Regression*
9	56	M	2	43	None	Regression*

*Includes both total and subtotal regression; CT, computed tomography

patients, all demonstrating regression of the cyst on computed tomography. Clinically six patients became symptom-free, two had reduced symptoms and one patient had unaltered symptoms after treatment. The results are summarized in *Table 2*. Two patients were operated upon after two and four treatments with alcohol respectively. This was due to the presence of multiple cysts and only moderate regression of cyst size as shown by computed tomography. Both operations were successful.

The mean hospital stay was 2·1 days per treatment.

Discussion

The treatment of non-parasitic liver cysts has been transformed during recent years from an aggressive surgical approach to non-operative treatment. Puncture and evacuation of cyst fluid alone leads to rapid recurrence of the liver cysts. Aspiration with injection of formaldehyde has been performed[7,8] but the relapse rate was high and concerns have been expressed about the potential damage to adjacent liver tissue[9]. Surgical treatment of liver cysts has been recommended, including local excision or formal liver resection[1,6]. In cases with bile-stained cyst contents, internal drainage into the gastrointestinal tract has been performed[10]; however, this can be complicated by cyst infection[3]. In polycystic liver disease, Lin *et al.*[11] described a new approach including excision of the outer wall of the most superficial cysts into which neighbouring deep cysts are successively fenestrated allowing free communication with the peritoneal cavity. This procedure has also proven successful for other investigators[3–5].

Improved radiological and imaging techniques such as ultrasonography and computed tomography can now provide us with detailed information about the size, number and location of liver cysts[12]. These procedures have also increased the number of cysts detected[13]. In the study by Bean and Rodan[14], six patients with non-parasitic hepatic cysts were treated with alcohol instillation into the cyst cavity, in five patients percutaneously under the guidance of ultrasonography and in one patient during laparotomy for a cholecystectomy. No recurrence was seen during a follow-up of 6–18 months. In our series of patients, we combined the use of computed tomography for diagnosis and localization of liver cysts with percutaneous aspiration of cyst fluid and injection of absolute alcohol to sclerose the cysts. The results seem promising, particularly since the procedure has not resulted in severe complications or signs of damage to liver tissue. The patients' discomfort is moderate, the hospital stay is short and the procedure can be repeated if necessary. Furthermore, in the future, when more experience has been gained, many patients can probably be treated on an out-patient basis.

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Surgical options in traumatic injury to the extrahepatic biliary tract

P. G. Bade, S. R. Thomson, A. Hirshberg and J. V. Robbs

Department of Surgery, University of Natal, Durban, South Africa

Correspondence to:
Mr S. R. Thomson, Department of Surgery, University of Natal Medical School, PO Box 17039,
Congella 4103, South Africa

A series of 53 patients who sustained extrahepatic biliary tract trauma were analysed to define the role of the various surgical options. Of the 45 patients with gallbladder injuries, 39 were due to stab wounds. Nine of the 45 injuries were repaired by primary suture without complication. Five patients underwent cholecystostomy and all developed biliary fistulae, which resulted in prolonged hospitalization. Cholecystectomy was performed in 31 patients; in retrospect many of these gallbladders could have been preserved because on only eight occasions was the gallbladder extensively damaged. Of eight extrahepatic bile duct injuries, the three partial transections managed by primary repair had a successful outcome, while the five complete transections were managed by a variety of techniques. Delayed diagnosis, failure of operative recognition of the injury and improper management were factors that led to mortality in two patients and prolonged morbidity in another. We conclude that suture repair is the operation of choice for gallbladder stab wounds without extensive injury. Ductal injury must be recognized. Partial transections are best managed by primary repair. Complete transections should be managed by primary duct jejunal anastomosis if the expertise is available.

Keywords: Gallbladder, extrahepatic bile ducts, trauma, operative management

Traumatic injury to the extrahepatic biliary tract is uncommon. The largest reported series consists of 40 patients[1]. Recommendations of operative management that are based on such small numbers of patients remain controversial. Although cholecystectomy is advocated for gallbladder injury[1–4], simple suture repair[5,6] or cholecystostomy[5] has also been advocated. Extrahepatic bile duct injury, though less common, presents a more complex operative problem with a greater potential for morbidity and mortality. At the Natal University affiliated hospitals, individual preference by various trauma surgeons led to the employment of a wide range of surgical procedures in the management of these injuries. This provided us with the opportunity to analyse these options and define their role in extrahepatic biliary tract trauma.

Patients and methods

All patients who sustained extrahepatic biliary tract trauma during the 5-year period 1984–1988 were identified by a computer-aided search using international, diagnostic and operative index codes. Their case records were scrutinized and the following data were extracted: demographic characteristics, mode of injury, clinical presentation, operative findings and treatment, associated injury, length of hospital stay, complications and follow-up. The overall pattern of presentation was analysed collectively but the subsequent management and outcome are discussed separately for the gallbladder and the bile duct injuries. A total of 53 patients (51 men and two women) were included in the series. The median age was 26 years (range 12–58 years).

Results

The 45 gallbladder injuries resulted from 39 stab wounds, five gunshot wounds and one blunt injury due to a motor vehicle accident. There were eight bile duct injuries: three stab wounds, one gunshot wound, and four due to blunt trauma. The blunt duct injuries were caused by a motorbike accident, an industrial accident, an assault, and a kick by a horse.

The presentation of extrahepatic biliary tract injury is shown in *Table 1*. Associated injuries were common and are detailed in *Table 2*. Thirty-five patients had hepatic injury and half the patients had two or more associated injuries. Only six patients had an isolated biliary injury. In two patients who sustained blunt trauma, recognition of their isolated injuries was delayed but did not adversely influence the outcome.

Nearly all the gallbladder stab wounds were through the body or fundus. Nineteen of the gallbladder injuries were described as small incised wounds and 18 were documented as through-and-through wounds. The surgical management and outcome of gallbladder injuries is shown in *Table 3*. Thirty-one patients were managed by cholecystectomy, nine by simple suture repair and five by cholecystostomy. All patients had

Table 1 *Presentation of extrahepatic biliary tract injury*

	Gallbladder	Duct
Acute		
Peritonitis	33	3
Shock	4	1
Evisceration*	6	0
Delayed (>24 h)		
Peritonitis	1	1
Jaundice	1	2
Biliary fistula	0	1

* Stab wound herniation of bowel or omentum

Table 2 *Biliary tract trauma: associated injuries*

	Biliary injury	
Associated injury	Gallbladder ($n=45$)	Duct ($n=8$)
Liver	30	5
Pleural space	7	1
Small bowel	6	0
Duodenum	5	0
Colon	5	1
Stomach	3	2
Pancreas	3	1
Kidney	3	0
Cardiac	3	0
Inferior vena cava	2	3
Portal vein	1	1
None	5	1

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Table 3 *Treatment of gallbladder injury*

Operation	Mode of injury: Stab	Mode of injury: Gunshot/blunt	Deaths	Average hospital stay (days)
Cholecystectomy	25	6	2	11
Suture repair	9	0	0	10
Cholecystostomy	5	0	0	17
Totals	39	6	2	

subhepatic drainage. Histology of the 31 gallbladders removed revealed extensive injury or intraluminal haematoma in only eight specimens, five of which resulted from gunshot wounds. There were two deaths, both attributable to associated injuries: a cardiac stab wound and a colonic injury. The latter was the only gallbladder injury where delay in diagnosis influenced outcome. Six patients developed a biliary cutaneous fistula; in five this was the direct result of cholecystostomy and in one it was due to a large parenchymal liver laceration. No complications resulted from suture repair of the gallbladder.

The average length of hospital stay is shown in *Table 3*. Patients treated by cholecystostomy stayed in hospital on average 7 more days than patients treated by either cholecystectomy or simple suture repair and this specifically represented the time taken for their biliary fistulae to close.

Table 4 depicts the site of injury, operative management and outcome of bile duct injuries. The three patients who had partial transections were treated by primary repair, with or without a T tube stent. They all recovered and none returned with jaundice or cholangitis.

Five patients had complete transections. Primary repair with T tube stenting and right hepatic lobectomy was the treatment in one patient with a complete transection at the confluence of hepatic ducts and severe liver parenchymal injury due to blunt trauma. He required reoperation to drain a large subhepatic bile collection and later a persistent intrahepatic cutaneous fistula associated with a confluence bile duct stricture was managed by fistulojejunostomy. Despite this he had recurrent cholangitis and died 17 months after initial presentation.

Late recognition of the bile duct injury occurred in the four remaining patients with complete transections. Cholecystjejunostomy with bile duct ligation was employed in the two common bile duct transections caused by blunt trauma. One recovered uneventfully, but, in the other, delay in diagnosis resulted in acute renal failure which complicated his otherwise successful recovery. In another patient, a complete transection due to a gunshot wound through the confluence of the hepatic ducts was not identified at operation because of a hilar liver laceration which was drained. This led to a biliary fistula, stricture, jaundice and a difficult late left hepaticojejunostomy.

The last patient presented to hospital with jaundice and biliary ascites, 3 weeks after an abdominal stab wound. His common hepatic duct transection was treated by hepaticojejunostomy. He subsequently died from septic complications of an anastomotic leak.

Discussion

Extrahepatic biliary tract trauma is usually diagnosed incidentally at laparotomy for penetrating or blunt abdominal injury[2]. The indications for operation are usually peritonitis or shock due to an associated injury. The presentation may be occult and isolated injury is frequently diagnosed late. In this series the delayed presentation of isolated injury was not deleterious to outcome. We and others[1,3] have found that the combination of delay with associated injury contributes significantly to morbidity and mortality. Early recognition is obviously desirable and a high index of suspicion is required so that the diagnosis may be established. Preoperative biliary scintigraphy may delineate the injury[7,8] and intraoperative cholangiography, when feasible, will identify the site of injury[1,9].

Recent reviews and current texts discussing the problem of penetrating gallbladder injury recommend cholecystectomy as the operative management of choice[1-4]. The rationale for cholecystectomy is that there may be contusion to the gallbladder of indefinite extent leading to necrosis, perforation and leakage following repair. The preserved traumatized gallbladder may undergo the cycle of infection, non-function and stone formation. There is no evidence in the literature to substantiate these claims. The rare complication of gallstone formation due to clot retention in the gallbladder as the result of blunt traumatic haemobilia has been described[10].

Options other than cholecystectomy which carry no risk of ductal injury merit serious consideration, in particular preservation of the injured organ. In our series, simple suture repair produced no bile leak or morbidity. The minor degree of gallbladder injury described in the operative record or at histological examination suggests that cholecystectomy could have been avoided in many patients and the gallbladder safely repaired.

Tube cholecystostomy has been recommended in unstable patients with other severe injuries where the surgeon considers cholecystectomy inadvisable[4]. The indication in this series was not intraoperative hypotension but simply the operating surgeon's preference. All gallbladder wounds managed by cholecystostomy were accompanied by prolonged bile leak, and this was the sole reason for prolonging hospital stay.

The most recent reported series advocating cholecystectomy for penetrating gallbladder injury[1,3] consist predominantly of gunshot wounds. In our series, 86 per cent of injuries were caused by stab wounds and in the majority these were incised wounds with minimal contusion, hence our recommendations have a more conservative bias. We advocate gallbladder preservation where feasible for stab wounds, and reserve cholecystectomy for the extensively injured gallbladder which is often due to gunshot injury.

The main factors that dictate the type of treatment in bile duct injury are the nature of the transection, whether partial or complete, and the patient's clinical condition.

Our experience with partial transections was such that they were all amenable to primary suture repair. All three patients had a good outcome and have not returned with complications. Several authors[1,9,11] confirm that simple partial transections treated by primary repair rarely give rise to biliary compli-

Table 4 *Outcome of bile duct injury related to site of injury, presentation delay and operative treatment*

Site	No. of patients	Operation	Outcome
Acute presentation			
Partial transections			
Common hepatic duct	1	Primary repair + stent	Uncomplicated
	1	Primary repair	Uncomplicated
Common bile duct	1	Primary repair	Temporary bile fistula
Complete transections			
Confluence of hepatic ducts	1	Primary repair	Morbidity, reoperations, death
Delayed presentation (>24 h)			
Complete transections			
Confluence of hepatic ducts	1	Drainage	Morbidity, late reconstruction
Common hepatic duct	1	Hepaticojejunostomy	Anastomotic leak, death
Common bile duct	1	Cholecystjejunostomy	Acute renal failure, recovered
	1	Cholecystjejunostomy	Uncomplicated

cations. In one of three partial transections, a T tube stent was used. In this instance, insertion of a T tube through a separate distal choledochotomy across the injury facilitated the repair of a small duct.

In the treatment of complete transections, end-to-end repair leads to a high incidence of stricture formation[11]. This is in part due to compromise to the axial blood supply of the duct caused by the transection and subsequent mobilization required to enable direct repair[12]. Complete transections are thus best managed by biliary enteric anastomosis. Most series[1,3,11] recommend Roux-en-Y duct jejunal anastomosis as providing the best long-term biliary drainage.

In this series and others[9,13] cholecystjejunostomy, the simplest of the operative options, has been employed with at least short-term success. The grounds for recommending this operation are tenuous because there is no long-term follow-up of its use in this setting, and a prospective study has shown that a duct–enteric anastomosis is superior to cholecystjejunostomy in the sustained relief of jaundice[14]. In essence, the gallbladder is an inferior conduit compared with the bile duct.

In the unstable patient where there are other complex injuries, or where the surgeon is inexperienced, an end tube choledochostomy secured to the proximal bile duct creates a controlled external fistula and allows rapid identification at reoperation.

In conclusion it is important to note that while associated injury was the main determinant of outcome in the group of patients sustaining gallbladder trauma, in those patients with bile duct injury, particularly if recognized late, the duct injury itself was pre-eminent in determining outcome. For gallbladder trauma we recommend primary suture repair for incised wounds without extensive injury, and feel it is an under-utilized option. Cholecystostomy has lesser merit as it results in prolonged biliary fistula. Cholecystectomy should be reserved for the more extensive gallbladder injury which usually results from gunshot wounds. In bile duct trauma, early recognition of the injury is essential if serious morbidity and mortality are to be avoided. Partial transections are safely repaired by primary suture. Complete transections are best managed by primary duct jejunal anastomosis if the operator is experienced and the patient stable.

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Changes in the hepatic perfusion index during the development of experimental hepatic tumours

D. M. Nott, S. J. Grime*, J. Yates, D. W. Day†, J. N. Baxter, S. A. Jenkins and T. G. Cooke

*University Departments of Surgery, *Nuclear Medicine and †Pathology, Royal Liverpool Hospital, Prescot Street, Liverpool, L69 3BX, UK*

Correspondence to: Mr. T. G. Cooke

A model of microscopic liver tumour has been developed in the Fisher rat by intraportal injection of $1{\cdot}6 \times 10^{7}$ Walker 256 carcinosarcoma cells. Rats were studied at 2, 4 and 6 days after the inoculation of live Walker cells. A control group received dead Walker cells. No tumour was visible in control groups at 2, 4 and 6 days after inoculation. Similarly in rats injected with live cells no tumour was visible at 2 days after inoculation but at 4 and 6 days the percentage hepatic replacement was (mean ± s.d.) 7·0 ± 2·3 and 27·9 ± 6·80 respectively. The hepatic perfusion index was significantly raised at 4 and 6 days after inoculation of live cells compared with control animals and those receiving viable cells after 2 days inoculation. Portal flow and portal venous inflow were significantly reduced when the hepatic perfusion index increased but hepatic arterial flow did not alter. Changes in the hepatic haemodynamics were accompanied by increases in the portal and splanchnic vascular resistance and an increase in the amount of arteriovenous shunting through the liver. These findings confirm studies that the hepatic perfusion index is useful in the detection of occult liver metastases but that the change is not a consequence of an increase in the hepatic arterial flow.

Keywords: Hepatic perfusion index, hepatic tumours, hepatic haemodynamics

The presence of overt hepatic metastases in patients with colorectal carcinoma is associated with a poor prognosis, most patients dying within 2 years of initial diagnosis[1,2]. Furthermore, approximately 30 per cent of patients with an apparently disease-free liver at the time of their initial laparotomy for colorectal carcinoma develop overt hepatic metastases within 2 years and again the prognosis is poor[3]. It has been suggested that effective therapy for hepatic metastases must be initiated in the early phase of their growth and development. This is supported by the observation that adjuvant portal vein infusion chemotherapy to the macroscopically disease-free liver at the time of resection of the primary colorectal tumour may reduce the incidence of liver metastases[4]. Therefore it is possible that early cytotoxic treatment for hepatic metastases may be effective in patients with occult liver metastases at the time of their initial laparotomy or alternatively where tumour cells have embolized to the liver during the mobilization and resection of the primary tumour.

Current imaging techniques such as computerized tomography, ultrasound scanning and static isotope imaging are not sensitive enough to detect metastases in their early stages of growth and development[5–7]. Recently, interest has focused on the use of dynamic hepatic scintigraphy for the early detection of hepatic metastases[8–12]. Using these techniques Leveson *et al.*[12] have shown that the hepatic perfusion index (HPI), the ratio of the hepatic arterial flow to total liver blood flow determined by dynamic hepatic scintigraphy, is altered in the presence of metastases and that alterations in the HPI predicted the presence of occult hepatic metastases with a sensitivity of 96 per cent.

The mechanism responsible for the alterations in the HPI cannot be established in man because of technical difficulties in accurately measuring the various components of liver blood flow. Therefore this study was undertaken to investigate the changes in the HPI and hepatic haemodynamics during the early stages of growth and development of hepatic tumour in an experimental animal.

Materials and methods

Induction of micrometastases

Walker 256 carcinosarcoma cells were grown in suspension in Williams E (Flow Laboratories Ltd., Rickmansworth, UK) medium supplemented with 5 per cent fetal calf serum at 37°C in a 5 per cent CO_2 atmosphere. Male Fisher rats weighing 290–340 g were anaesthetized with intraperitoneal sodium pentobarbitone ($6\,mg\ 100\,g^{-1}$ body weight). Through a midline incision the portal vein was exposed and 0·2 ml of a suspension of 8×10^{7} Walker cells per millilitre were injected intraportally over 10 s with a 2 Fr gauge needle. The needle was held in position in the portal vein for approximately 30 s after completion of the injection to minimize the risk of spillage of the Walker cells into the peritoneal cavity. Haemostasis was achieved by compression of the portal vein for 30 s. A control group of rats was inoculated similarly with the same number of Walker cells killed by temperature reduction. The laparotomy was closed in two layers and the rats were studied at 2, 4 and 6 days after inoculation of either viable or dead Walker cells.

Radionuclide studies

The method for deriving the hepatic perfusion index in the rat is described in detail elsewhere[13]. Briefly, rats were fasted for 24 h but allowed water *ad libitum* and were anaesthetized with intraperitoneal sodium pentobarbitone. The right carotid artery was cannulated with a 10 cm 2 Fr Portex (London, UK) cannula which was screened into the left ventricle using a Siemans Siremobile (Siemans Ltd., Sunbury-on-Thames, UK) image intensifier. Adequate expulsion of a left ventricular bolus was assessed by the injection of 0·1 ml of sodium meglumine. The rats were then placed supine under an NE 8900 γ camera (Nuclear Enterprises Ltd., Edinburgh, UK) with a 1 cm ($\frac{1}{4}$ inch) pin hole collimator linked to a PDP DEK computer (Digital Equipment Corporation, Maynard, Massachusetts, USA). ^{99m}Tc sulphur colloid (0·04 ml) was injected rapidly as a bolus into the left ventricle and images acquired at 3 frames per second for 30 s and stored on hard disc. A composite image of the first 5 frames of each study was constructed and regions of interest (ROI) were drawn around the left ventricle, right kidney and right lobe of the liver avoiding the superior pole of the kidney and lower border of the lung (*Figure 1*). Time–activity curves were then generated from these ROIs and each curve was subjected to a maximum of three quadratic smooths. Typical time–activity curves for control rats

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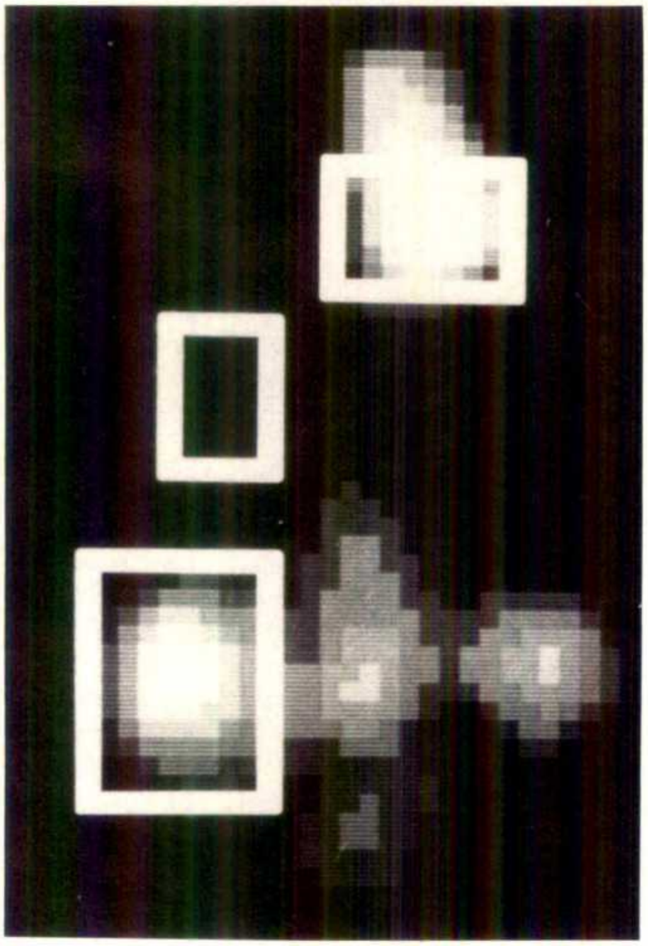

Figure 1 *Composite image obtained by dynamic scintigraphy after the rapid intraventricular injection of 0·04 ml ^{99m}Tc-sulphur colloid showing regions of interest drawn around the heart, liver and right kidney*

are shown in *Figure 2*, and for rats with microscopic hepatic tumours in *Figure 3*.

The HPI was derived from the gradients of the arterial (G_1) and portal phases (G_2) of the liver perfusion curves (*Figure 2*). The left ventricle and right kidney curves were used as the timing reference for the two perfusion phases. The hepatic arterial phase was considered to begin with the start of the kidney arterial phase and extend to the peak of the kidney time–activity curve. The portal inflow phase was assumed to extend from the peak of the kidney curve to either the point of recirculation or to a point at which the kidney time–activity curve reached a plateau.

Haemodynamic measurements

Microsphere technique. Immediately after the completion of the scintigraphic studies the right and left femoral arteries were cannulated using 2 Fr Portex cannulae. The right femoral artery cannula was connected to a Sage 351 (Orien Research Incorporated, Cambridge, Massachusetts, USA) withdrawal pump. The left femoral artery cannula was connected to a physiological pressure transducer for the continuous measurement of arterial blood pressure. A reference blood sample was withdrawn from the femoral artery over a 70-s period. Ten seconds after the start of the blood withdrawal the rats received an intraventricular injection of 60 000–80 000 ^{57}Co Nen-Trac microspheres (New England Nuclear, Stevenage, UK), $16·4 \pm 1$ µm diameter suspended in 0·9 per cent normal saline with 0·01 per cent tween in a volume of 0·4 ml over 20 s.

The animals were killed with an overdose of pentobarbitone 5 min after the microsphere injection. The organs were removed, weighed and the radioactivity counted in a Philips well counter (Pye Unicam Ltd., Cambridge, UK). Cardiac output and liver blood flow were determined by the method of McDevitt and Nies[14]. Portal venous inflow was calculated by adding together the flows to the spleen, pancreas and splanchnic organs. If the blood flow to the right and left kidney was >10 per cent the distribution of the microspheres was not considered to be uniform and the results discarded.

Electromagnetic flowmetry. In further groups of rats inoculated with live or dead Walker cells, a cannula connected to a pressure transducer was placed in the right femoral artery for measurement of arterial blood pressure after the scintigraphic measurements. Through a midline incision the hepatic artery and portal vein were mobilized. Electromagnetic flow probes (Gould Medical Ltd., Lutterworth, UK) were then placed around the portal vein, cranial to its junction with the pancreaticoduodenal vein and around the hepatic artery and zeroed *in vivo* by occluding the vessels distal to the probes. Blood flow in both the portal vein and the hepatic artery were recorded using a Gould Flowmeter (Model SP2202) (Gould Medical Ltd., Lutterworth, UK).

Portal pressure studies. Immediately after measurement of the portal venous and hepatic artery flow, the portal vein was cannulated retrogradely with a 2 Fr paediatric venous cannula 2 cm below the porta hepatis so that the tip of the cannula lay just above the confluence of the splenic and portal veins. The cannula was attached to a pressure transducer to measure portal pressure. No mobilization of the liver was

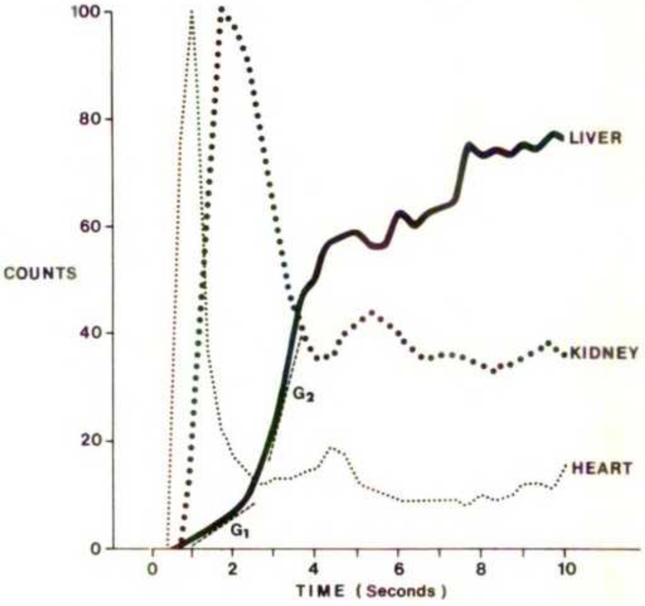

Figure 2 *Typical time–activity curves for control rats showing the derivation of the hepatic perfusion index from the gradients of the hepatic arterial (G_1) and portal venous phases (G_2): hepatic perfusion index = $G_1/(G_1 + G_2)$*

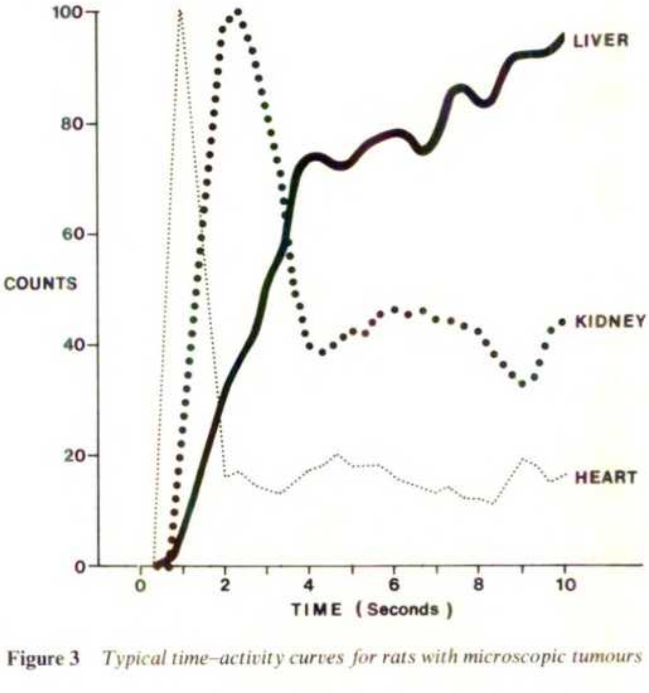

Figure 3 *Typical time–activity curves for rats with microscopic tumours*

required for the procedure and hepatic trauma was avoided during insertion of the cannulae

Splanchnic and portal vascular resistances were calculated from the following equations.

$$\text{Splanchnic vascular resistance (mmHg min ml}^{-1}) = \frac{\text{Mean arterial blood pressure (mmHg)}}{\text{Portal venous flow (ml min}^{-1})}$$

$$\text{Portal vascular resistance (mmHg min ml}^{-1}) = \frac{\text{Portal pressure (mmHg)}}{\text{Portal venous flow (ml min}^{-1})}$$

Measurement of intrahepatic arteriovenous shunting Further groups of tumour-bearing and control rats were anaesthetized with sodium pentobarbitone and through a midline incision the coeliac, hepatic, gastroduodenal and pancreaticoduodenal arteries were exposed The distal gastroduodenal artery was ligated with 7/0 silk at its junction with the pancreaticoduodenal artery, a 10 cm long 2 Fr Portex cannula was inserted via an arteriotomy up to the junction of the coeliac and hepatic arteries and the hepatic arterial pressure was recorded via a pressure transducer. A sodium iodide scintillation detector was then placed over the rat's thorax and screened from the abdomen using a lead shield. Under direct vision with the aid of an operating microscope 1 MBq of 40 μm ^{99m}Tc-macroaggregated albumin in a volume of 0·05 ml was manually injected into the hepatic artery, over a period of 10 s, at physiological pressures using a high pressure liquid chromatography syringe. The amount of radioactivity passing to the lungs was measured by the scintillation counter.

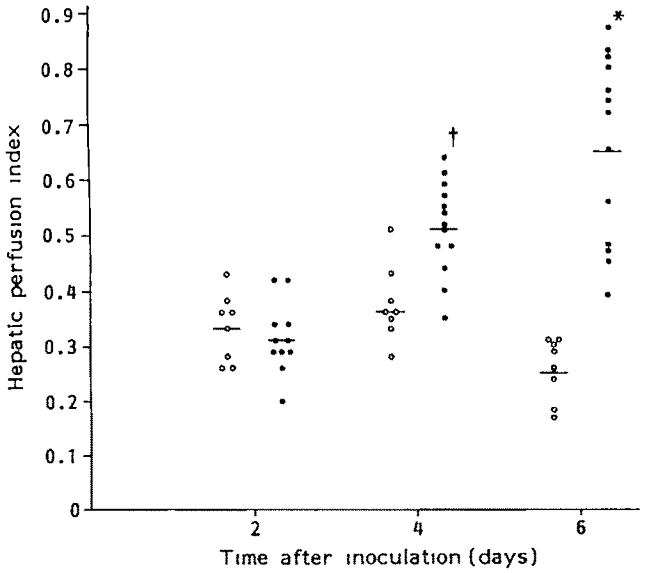

Figure 4 *Hepatic perfusion index values of rats inoculated with live* (●) *or dead* (○) *Walker cells at 2, 4 and 6 days after inoculation* *P<0·01, †P<0·05 (versus *day 2*)

Microscopy. Livers from all rats were fixed in formol saline and sections of 4 μm thickness cut at 1 mm intervals throughout the entire liver Sections were stained with haematoxylin and eosin and the percentage hepatic replacement of the liver was determined using the point sampling technique. Slides were projected on to a large graph paper screen and metastases that fell on the intersects of the graph were counted, allowing accurate quantification of the amount of tumour present.

Statistical analysis

The gradients of the time–activity curves were derived by a least squares analysis for a straight line The comparison of data between groups was achieved by a one-way analysis of variance (ANOVA)

Results

Histopathology

Metastases were not apparent microscopically 2 days after inoculation of the carcinosarcoma cells, only an occasional Walker cell being observed within the portal triads. However discrete micrometastases with a mean diameter of between 100 and 150 μm were present by day 4 after inoculation and these had increased in size by day 6 to 250–350 μm By day 4 the percentage hepatic replacement was 7·0±2·3 (mean ±s.d.) rising to 27·9±6·80 by day 6. No tumour was visible in control animals at any time interval after injection of dead cells.

Hepatic perfusion index

The hepatic perfusion index of control rats receiving dead cells did not change significantly at any time after inoculation. Similarly in rats receiving viable Walker cells, the index at 2 days was not significantly different from controls. There was a significant increase in the HPI at 4 and 6 days in rats inoculated with viable tumour compared with controls and compared with the 2 day stage when no demonstrable tumour growth was evident (*Figure 4*).

Changes in hepatic haemodynamics

No change in portal venous inflow, hepatic artery flow, portal pressure, splanchnic vascular resistance or portal venous resistance was observed in control rats measured by either the microsphere or electromagnetic techniques. The hepatic artery flow did not alter during the growth of the hepatic tumours but the portal venous inflow was significantly decreased at day 4 and at day 6 (P <0·001, ANOVA) compared with the values at day 2 or at any time for control animals injected with dead cells (*Table 1*).

Table 1 *Hepatic and systemic haemodynamics in control rats and rats with developing hepatic tumour by the microsphere technique*

	Time after inoculation (days)					
	2 days		4 days		6 days	
Organ	Control (n=10)	Tumour (n=13)	Control (n=10)	Tumour (n=13)	Control (n=7)	Tumour (n=15)
Hepatic artery flow (ml min^{-1} g^{-1})	0·39±0·05	0·36±0·09	0·36±0·09	0·32±0·08	0·38±0·09	0·35±0·07
Spleen (ml min^{-1} g^{-1})	1·54±0·52	1·85±0·54	1·65±0·86	0·81±0·53*	1·49±1·01	0·76±0·44*
Portal venous inflow (ml min^{-1} g^{-1})	1·13±0·39	1·00±0·20	1·15±0·38	0·71±0·22*	1·06±0·25	0·66±0·08*
Lungs (ml min^{-1} g^{-1})	0·68±0·19	0·93±0·58	0·79±0·39	0·76±0·35	0·79±0·35	0·70±0·49
Cardiac output (ml min^{-1})	75·82±10·57	70·95±5·70	68·14±7·60	68·69±5·76	70·66±10·42	75·57±8·86

Results are expressed as mean ±s.d. *P<0·001 (*versus* control)

Table 2 *Hepatic artery and portal vein flow in control rats and rats with developing hepatic tumour measured by electromagnetic flowmetry*

	Time after inoculation (days)					
	2 days		4 days		6 days	
	Control ($n=6$)	Tumour ($n=7$)	Control ($n=6$)	Tumour ($n=7$)	Control ($n=6$)	Tumour ($n=8$)
Hepatic artery flow (ml min^{-1})	2·96±0·29	2·94±0·38	3·41±0·60	3·00±0·46	3·33±0·55	2·76±0·56
Portal venous flow (ml min^{-1})	15·50±1·11	16·0±2·00	15·1±3·35	9·00±1·36*	16·6±0·74	8·25±2·04*

Results are expressed as mean ±s.d. * $P<0·001$ (*versus* control)

Table 3 *Portal pressure, portal venous and splanchnic vascular resistance of control rats and rats with developing hepatic tumour*

	Time after inoculation (days)					
	2 days		4 days		6 days	
	Control ($n=6$)	Tumour ($n=7$)	Control ($n=6$)	Tumour ($n=7$)	Control ($n=6$)	Tumour ($n=8$)
Splanchnic vascular resistance (mmHg min ml^{-1})	6·91±1·12	6·97±1·97	6·10±0·77	11·48±1·96†	6·77±0·75	12·81±3·92†
Portal venous resistance (mmHg min ml^{-1})	0·43±0·10	0·51±0·09	0·57±0·16	0·99±0·12†	0·45±0·04	1·03±0·22†
Portal pressure (mmHg)	6·83±1·57	7·85±0·98	8·83±2·35	8·77±0·40	7·58±1·05	8·45±1·81*

Results are expressed as mean ±s.d. * $P<0·05$; † $P<0·001$ (*versus* control)

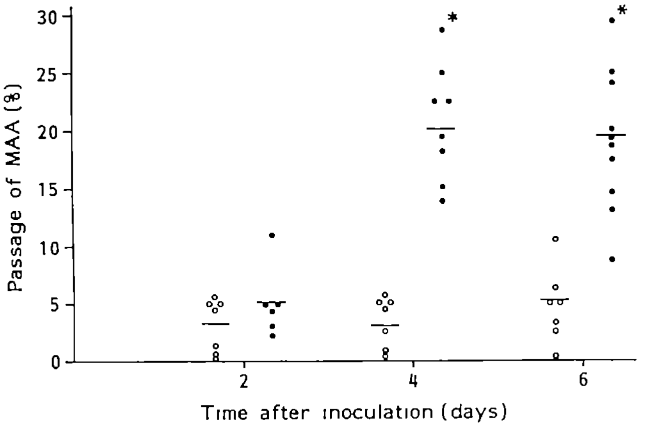

Figure 5 *Percentage passage of microaggregated albumen (MAA) through the liver of rats inoculated with live (●) or dead (○) Walker cells at 2, 4 and 6 days after inoculation.* *P<0·01 (versus *day 2*)

The alterations in hepatic haemodynamics were reproduced by the electromagnetic flow studies which confirmed that there was no change in hepatic artery flow but there was a significant decrease in portal venous flow at day 4 and day 6 after injection of viable Walker cells compared with controls (*Table 2*). The reduction in portal flow at 4 days and at 6 days after inoculation of Walker cells was accompanied by an increase in portal pressure at day 6. Consequently portal vascular resistance and splanchnic vascular resistance were significantly raised at 4 and 6 days (*Table 3*)

Intrahepatic shunting

The passage of microaggregated albumin through the liver did not change in control rats or in the first 2 days after inoculation of viable cells. However at 4 and 6 days there was a significant increase in the passage of microaggregated albumin through the liver compared with the 2-day stage and control animals, indicative of increased intrahepatic shunting with the growth and development of tumour (*Figure 5*).

Discussion

The results of this study in the rat confirm observations in man that the hepatic perfusion index changes during the growth and development of hepatic tumours and may therefore be of diagnostic value in the detection of occult liver micrometastases. It has been assumed that the change in the hepatic perfusion index during the development of hepatic metastases is related to an increase in hepatic arterial flow. This hypothesis was based on observations that liver metastases initially derive their blood supply from the portal vein, but as they increase in size, neovascularization occurs with the formation of both portal and arterial elements. With continued growth of the tumour the portal vessels become compressed and the more tensile arteries provide up to 90 per cent of the tumour's blood supply[15–19]. There have, however, been few detailed studies of the changes in hepatic haemodynamics during the development of liver metastases.

In the present study hepatic tumour was induced in rats by the injection of $1·6\times10^7$ Walker 256 carcinosarcoma cells directly into the portal vein; although this volume of cells may appear to be large it did result in a reproducible model of hepatic tumour in the rat. In order to establish whether an injection of a large number of cells into the liver might influence hepatic haemodynamics by a mechanical effect, the control group animals received the same number of dead cells. Throughout the experiment there were no significant differences in any aspect of haemodynamics in rats inoculated with dead cells at any of the times studied. Furthermore, no alterations in hepatic haemodynamics were observed 2 days after the inoculation of viable cells. Haemodynamic changes were only apparent at 4 and 6 days when liver tumour was histologically evident. It would appear that the relatively large number of cells used in this study to produce liver tumour had no lasting effect on hepatic haemodynamics.

Two haemodynamic methods were used to investigate the change in the hepatic perfusion index during the development of tumours, the use of microspheres to quantify absolute changes in hepatic artery flow and portal venous inflow and electromagnetic flowmetry to determine relative changes in hepatic artery and portal venous flow. The results clearly indicate that the changes in the hepatic perfusion index are a consequence of a decreased portal venous inflow. In all experiments hepatic artery flow did not alter This observation contradicts the hypothesis proposed by Leveson *et al.*[12] who suggested that the alteration of the hepatic perfusion index in the presence of hepatic metastases is due to an increase in total hepatic artery flow. As portal flow decreased with the development of liver tumours, portal pressure increased and consequently splanchnic vascular resistance and portal venous resistance were also signficantly elevated. This change in outflow resistance was reflected by a reduction in intestinal and splenic blood flow and consequently a reduction in portal venous inflow. The decrease in portal inflow with the development of liver tumour could be due to either arteriovenous shunting or a mechanical effect resulting from compression of the portal triad by the tumour. The possibility of a simple mechanical effect of the tumour cannot be discounted, but is difficult to demonstrate experimentally

In the present study increased passage of ^{99m}Tc microaggregated albumin through the liver occurred at 4 and 6 days after inoculation of viable Walker cells suggesting that the increase in portal resistance could be due, at least in part, to the development of new arteriovenous shunts within or surrounding the tumours rather than at pre-existing presinusoidal arterioportal communications[18]. The presence of unidirectional arterioportal shunting has previously been reported by Geumei *et al.*[20] and casting studies have demonstrated that neovascularization is well developed by the time metastases have grown to 1 mm in diameter[21]. Of particular relevance to the present study is the observation that viable tumour is only present 4 days after direct injection of Walker cells into the liver parenchyma. At this stage of development, blood vessels supplying the tumour display a remarkable tortuosity and distribution and by day 6 there is evidence of an increased blood supply to tumour, the new vessels being characterized by their irregular size and the presence of anastomotic connections between them

This study confirms previous observations in man that the hepatic perfusion index does alter with the presence of micrometastases. The change in the index is secondary to a reduction in portal venous inflow consequent on an increased portal vascular resistance Hepatic artery flow does not increase during the early stages of hepatic tumour development but an increase in arterioportal shunting occurs even in tumours as small as 150 μm in diameter. Alteration in the hepatic perfusion index appears, therefore, to be a sensitive method for the early detection of hepatic metastases before they are large enough to be diagnosed by conventional imaging techniques It is possible that micrometastases may be more sensitive to cytostatic therapy than larger liver secondaries and hence early detection would be of advantage. Clearly, further studies are required to substantiate this hypothesis.

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Direct retroperitoneal approach to necrosis in severe acute pancreatitis

P.-L. Fagniez, N. Rotman and M. Kracht

Department of General Surgery, Hôpital Henri Mondor, 51 Avenue du Mal de Lattre de Tassigny, 94010 Créteil, France

Correspondence to. Professor P.-L. Fagniez

From 1981 to 1987, 40 patients with severe acute pancreatitis were operated on using a direct retroperitoneal approach, 22 primarily and 18 after a first operation performed through another incision. The severity of the disease was assessed by Ranson's bioclinical and computed tomography scan scoring systems. The retroperitoneal approach consisted of a left lateral incision, just anterior to the 12th rib, allowing direct access to the pancreas and a complete manual exploration of the gland and peripancreatic spaces. All patients but one were operated on for infected necrosis. The overall mortality rate was 33 per cent but was lower in the patients operated on primarily through a direct retroperitoneal approach (18·2 per cent). Twenty patients (50 per cent) developed a local complication (haemorrhage, colon fistula and/or necrosis). The direct retroperitoneal approach permits the removal of necrosis and several reoperations without the risk of large wound dehiscence and does not preclude the extension of the incision to a subcostal incision when necessary.

Keywords: Severe acute pancreatitis, surgical treatment

Although necrosis is found in only 4–16 per cent of all patients with acute pancreatitis, most of the patients with a necrotizing form of pancreatitis will require surgery in the course of the disease[1–3]. The rationale for the surgical drainage of pancreatic necrosis is (1) the early removal of activated pancreatic enzymes, endotoxins and vasoactive products responsible for multiple organ failure[3] and (2) the avoidance of infection of necrosis which is a major cause of death and which has been reported to occur in almost 80 per cent of patients surviving longer than 7 days[4].

The extent of the surgical procedure in necrotizing pancreatitis has been widely debated over the years; various attitudes have been proposed from extensive pancreatectomy[5–8] to limited débridement of necrosis[1–3,9,10]. We report here our experience of the surgical treatment of severe acute necrotizing pancreatitis using a direct retroperitoneal approach.

Patients and methods

Patients

From 1981 to 1987, 40 patients with severe acute pancreatitis were operated on using a retroperitoneal approach. These patients represent 27·2 per cent of the patients hospitalized for acute pancreatitis (during the study period 147 patients were treated in our hospital for mild acute pancreatitis). There were 30 men and 10 women. Their ages ranged from 26 to 80 years (median 46 years). The main cause of pancreatitis was alcohol (26 patients). Nine patients had pancreatitis related to gallstones, three patients had postoperative pancreatitis, one had a carcinoma of the head of the pancreas and in one case the aetiology of the pancreatitis could not be determined. The severity of the pancreatitis was assessed by the Ranson criteria score in 31 patients[11]. The median value for the bioclinical criteria was four: eight patients had three prognostic signs, seven patients had four, seven patients had five, five patients had six and one patient each had one, two, seven and eight prognostic signs. In nine patients, referred from other hospitals, one or more of the bioclinical criteria were missing and the severity score could not be established. All the patients had at least one contrast-enhanced computed tomography (CT) scan before operation. CT scans were performed using a Somatom Siemens SF (Siemens Medical Engineering Group, Erlangen FRG) with a 4·5 s scan time and a section thickness of 10 mm. Patients were given 1 litre water-soluble contrast medium orally or through a nasogastric tube before the examination. CT scans were performed before and after an intravenous bolus injection of 60 ml contrast medium. The average number of CT scan examinations per patient (pre- and postoperatively) was four. CT scans were graded according to Ranson's classification[12]. Thirty-nine patients had a grade E (two or more fluid collections) contrast-enhanced CT scan; one patient was grade D (one fluid collection). Percutaneous aspiration of peripancreatic fluid was performed under CT scan guidance in ten patients at our institution. In all cases it yielded fluid for bacteriological analysis.

Twenty-four patients were referred from other institutions, 18 after being operated on. Twenty-two patients (six referred and 16 hospitalized primarily at our institution) were operated on primarily in our hospital.

Clinical management

All patients were admitted to an intensive care unit. Medical treatment included nasogastric suction, total parenteral nutrition and cardiac monitoring. Antibiotics were administered only to patients with proven bacterial infection. Mechanical ventilation was necessary for more than 48 h in 19 patients. Peritoneal dialysis was performed in ten patients presenting with hypotension (< 100 mmHg) or severe abdominal pain with diffuse guarding at the time of admission. The median duration of dialysis was 1·9 days. Eight patients were treated by drainage under CT guidance. Percutaneous drainage was performed before operation in five patients and in three patients for residual peripancreatic collections after a first operation. The aim of the percutaneous drainage was to avoid operation in patients with homogeneous, low density collections which were thought to consist of infected fluid without debris. Surgery was considered in three circumstances: (1) deterioration of renal, pulmonary or cardiac function despite medical treatment (16 patients); (2) septic shock unexplained by a source of infection other than an abdominal abscess (14 patients), (3) the recovery of infected fluid under CT scan guidance and/or the failure of percutaneous drainage (ten patients).

Surgical technique

The retroperitoneal approach to the pancreas was conducted through a left lateral subcostal incision, 10–15 cm in length, located just anterior to the 12th rib. The peritoneal attachments of the upper part of the descending colon were then divided allowing direct access to the pancreas (*Figure 1*). In four patients with collections and necrosis developing in the right mesocolon and the right pararenal spaces, a similar right subcostal incision was used; in these cases the retroperitoneum was reached after mobilization of the ascending colon. The whole pancreas, from tail to head, as well as the peripancreatic spaces were explored by manual palpation. All pancreatic and peripancreatic necrosis and fluid collections were removed by blunt dissection and the apparently healthy part of the pancreas was left in place. The retroperitoneum was drained by one or two tube drains. In 14 patients continuous irrigation of the retroperitoneum was performed by means of

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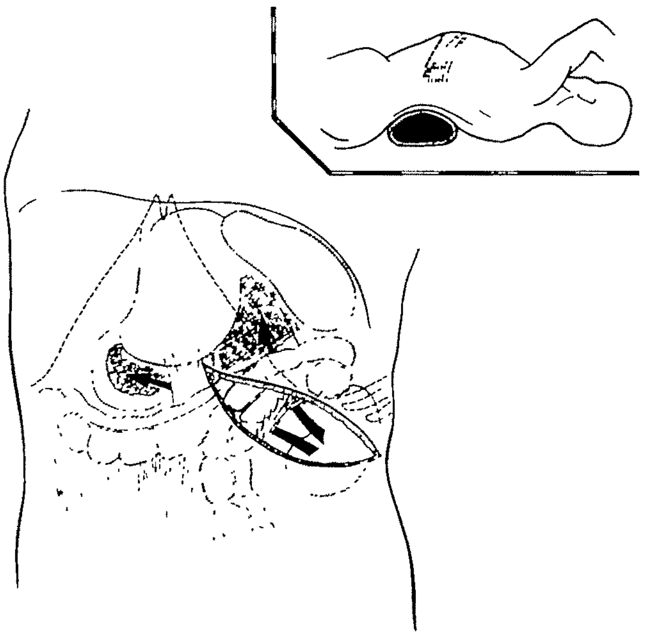

Figure 1 *A left posterior subcostal incision (top, right) allows a direct retroperitoneal approach to the pancreas after division of the attachments of the descending colon (bottom, left)*

a double-lumen nasogastric suction tube. The other patients had discontinuous irrigation by drains. The solution used for lavage was a 10 per cent solution of povidone-iodine

Six patients had a cholecystectomy, two patients had a cholecystectomy with common bile duct drainage, and five had a cholecystostomy. These procedures were performed at the first operation and mainly in patients referred from other institutions. Only two patients admitted primarily to our hospital underwent a biliary procedure (one cholecystostomy and one cholecystectomy).

Results

The limited retroperitoneal approach through a left lateral subcostal incision allowed complete exploration of the pancreas in all patients. Thirty-five patients (88 per cent) had pancreatic and peripancreatic necrosis. The parenchymal necrosis was located in most patients at the periphery of the gland, leaving a healthy central part. Only one patient had complete necrosis of the head of the pancreas. In all patients but one the necrosis was infected. The most common organisms cultured were Gram-negative bacteria (*Tables 1* and *2*). Four patients had infected fluid collections with minimal necrosis. One patient had a sterile fluid collection. Infection was present at the first operation in 18 patients. In 21 patients infection was disclosed at the second operation. in ten cases it was a superinfection as the material yielded from the first operation was sterile while in 11 cases bacteriological findings from the first operation were not available. At the time that infection was diagnosed only two patients had a colonic fistula. In three patients the presence of fluid collections and necrosis in the right pararenal anterior space and right mesocolon required further débridement through a right limited incision.

The average number of operations per patient was 3·6 (range 1–9). Eight patients had only one operation. The median timing of the first operation was 14 days after the onset of the disease for the patients operated on at our hospital. Patients operated on before referral underwent their first operation after a median time of 3 days

Five patients developed general complications without local complications. Twenty patients (50 per cent) developed local complications (*Table 3*). Haemorrhage occurred in eight patients. In five cases it was limited to a diffuse oozing from the retroperitoneum and was treated successfully by packing. Three patients had major haemorrhage resulting in cardiocirculatory failure in the operating room. Packing stopped the haemorrhage in one case. In the two other patients the limited incision had to be extended to a bilateral subcostal incision to control the haemorrhage. One patient had a splenectomy for a spontaneous splenic haematoma.

Left colonic fistula, related to the repeated mobilization of the left colon, developed in eight patients and was treated by right transverse colostomy This was closed after healing of the fistula had been confirmed by barium enema. In one patient the fistula did not close despite the colostomy, and it was closed surgically. One patient had a pancreatic fistula which healed spontaneously after 6 months. One patient had a gastric fistula but died of multiple organ failure with no treatment of the

Table 1 *Organisms cultured from primarily infected peripancreatic collections in 15 patients*

Patient	Primary infection	Patient	Primary infection
1	*Staphylococcus albus*		*Staphylococcus aureus*
2	*Enterobacter cloacae*	9	*Proteus mirabilis*
3	*Escherichia coli*	10	*Staphylococcus aureus*
	Proteus morgani	11	*Escherichia coli*
	Staphylococcus aureus	12	*Serratia marcescens*
	Streptococcus faecalis	13	*Escherichia coli*
4	*Escherichia coli*		*Pseudomonas*
5	*Escherichia coli*		*Serratia marcescens*
	Enterobacter cloacae	14	*Escherichia coli*
6	*Escherichia coli*	15	*Staphylococcus aureus*
	Serratia marcescens	16	*Klebsiella pneumoniae*
	Streptococcus faecalis		*Staphylococcus epidermidis*
	Pseudomonas	17	*Pseudomonas*
	Klebsiella pneumoniae		*Citrobacter*
7	*Bacteroides fragilis*		*Staphylococcus aureus*
	Streptococcus milleri	18	*Acinetobacter*
	Klebsiella pneumoniae		*Streptococcus faecalis*
	Fusobacterium		*Staphylococcus aureus*
8	*Escherichia coli*		*Candida*

Table 2 *Organisms cultured at the second operation from peripancreatic collections in 21 patients*

Patient	Secondary infection	Patient	Secondary infection
1	*Serratia marcescens*	12	*Proteus mirabilis*
	Pseudomonas		*Klebsiella pneumoniae*
2	*Staphylococcus aureus*		*Acinetobacter*
	Escherichia coli		*Streptococcus faecalis*
	Streptococcus faecalis	13	*Streptococcus faecalis*
3	*Escherichia coli*		*Pseudomonas*
	Staphylococcus aureus		*Acinetobacter*
4	*Escherichia coli*	14	*Escherichia coli*
	Pseudomonas		*Enterobacter cloacae*
	Streptococcus faecalis	15	*Proteus morgani*
5	*Escherichia coli*		*Enterobacter cloacae*
	Pseudomonas	16	*Pseudomonas*
	Streptococcus faecalis		*Klebsiella pneumoniae*
	Enterobacter cloacae	17	*Streptococcus faecalis*
	Klebsiella pneumoniae		*Pseudomonas*
6	*Escherichia coli*		*Staphylococcus aureus*
7	*Escherichia coli*	18	*Streptococcus faecalis*
	Proteus mirabilis		*Proteus morgani*
	Bacteroides		*Klebsiella pneumoniae*
8	*Escherichia coli*		*Streptococcus milleri*
	Staphylococcus aureus		*Staphylococcus aureus*
9	*Enterobacter cloacae*	19	*Streptococcus faecalis*
	Pseudomonas		*Pseudomonas*
10	*Escherichia coli*	20	*Escherichia coli*
	Pseudomonas		*Proteus mirabilis*
	Acinetobacter		*Candida*
11	*Klebsiella pneumoniae*	21	*Escherichia coli*
	Acinetobacter		*Streptococcus faecalis*
	Staphylococcus aureus		

Table 3 *Local and general complications*

Patient	Local complications	General complications
1	Left colonic fistula	Respiratory failure
2	Left colonic fistula Right colon necrosis	
3	Haemorrhage	Multiple organ failure
4	Haemorrhage	Multiple organ failure
5	Left colonic fistula	Respiratory failure
6	Haemorrhage	Multiple organ failure
7	Transverse colon necrosis	Multiple organ failure
8	Gastric fistula	Multiple organ failure
9	Splenic haematoma	Respiratory failure
10	Left colonic fistula	
11	Left colonic fistula	Pneumonia
12	Haemorrhage Transverse colon necrosis	Multiple organ failure
13	Left colonic fistula	
14	Left colonic fistula Haemorrhage	Respiratory failure
15	Haemorrhage	Respiratory failure
16	Left colonic fistula	
17	Haemorrhage	
19	Pancreatic fistula	
20	Haemorrhage Bleeding duodenal ulcer	
21		Respiratory failure
22		Respiratory failure
23		Respiratory failure
24		Infected pleural effusion
25		Multiple organ failure

fistula. One patient had a major haemorrhage from a posterior duodenal ulcer which required surgery Two patients had a transverse colon necrosis and one had a necrosis of the right colon related to an anterior extension of the inflammatory process with thrombosis of the colonic vessels.

Thirteen patients died (33 per cent) Two patients died from complications of mechanical ventilation (acute airway obstruction and tracheal necrosis) Two patients died from pulmonary embolism with no progressive pancreatitis. One patient died from massive haemorrhage from the portal vein which could not be controlled. One patient died from a carcinoma of the head of the pancreas which was the cause of the pancreatitis; in this patient the inflammatory process had subsided at the time of death. Seven patients died from multiple organ failure The median time of death was 58 days. Only four patients out of the 22 operated on primarily at our institution died (18·2 per cent); one of these patients died from pulmonary embolism.

Three out of seven patients with multiple organ failure died without continuing pancreatitis from septicaemia due to *Candida albicans*. The other four died with progressive necrotizing pancreatitis. The overall hospital stay for survivors and non-survivors was 70 ± 38 days. Nine patients developed a wound hernia which was repaired 6–12 months after hospital discharge. Only two patients became diabetic and required permanent insulin treatment.

Discussion

Necrotizing pancreatitis is characterized by haemorrhagic necrosis of the gland and by fatty and haemorrhagic necrosis of the peripancreatic spaces Most often the necrotizing process remains enclosed in the retroperitoneum and develops to the left and anteriorly. It seemed to us that a direct retroperitoneal approach to the pancreas would be the best way to remove necrosis and to achieve adequate direct drainage of collections and necrosis[13] This type of approach allows complete exploration of the gland and peripancreatic spaces but precludes a formal pancreatectomy. Some authors advocate extensive pancreatectomy[5–7] in order to limit the general and local complications of the disease, but these procedures carry a high mortality rate (30–50 per cent) and do not completely prevent the occurrence of pancreatic abscesses[6,14]. On the other hand, there is a trend towards a restriction of the indications of surgery[13,15–17]. However, in a deteriorating patient with signs of severe sepsis or multiple organ failure unexplained by extra-abdominal causes, surgery cannot be postponed.

The advantages of a retroperitoneal approach are multiple it can be used for several reoperations without the disadvantages of a large wound dehiscence, it can be performed in patients previously operated on through a transperitoneal approach, it allows the scooping out of all necrotic and purulent material, and it does not preclude the extension of the incision to a right or bilateral subcostal incision. This situation was met in five patients: one with massive haemorrhage, one with haemorrhage from the portal vein and transverse colon necrosis, one with a bleeding duodenal ulcer and two with colon necrosis Some authors advocate wide exploration of the entire abdomen in order not to overlook a necrotic collection[10,16]. In our series, CT scanning, which was performed in every patient, allowed precise preoperative localization of the necrotic collections[13].

The two drawbacks of our method are colonic fistulae due to the repeated mobilization of the descending colon and wound hernias We observed eight colonic fistulae attributable to the surgical procedure This complication occurred at the beginning of our experience because of insufficient dissection of the left colon attachments. No patient died from this complication. Wound hernias are caused by incomplete closure of the wound, the drains being brought out through the incision. Nine patients developed a wound hernia which was repaired 6–12 months after hospital discharge.

Another theoretical disadvantage of this method is that no biliary procedure can be performed; 85 per cent of the biliary procedures in our patients were performed in other institutions. Actually, there was no evidence that the biliary procedures improved survival It seems that once severe acute pancreatitis is initiated, the prognosis relies on its evolution, and that the removal of common bile duct stones may not really influence survival. This is in accordance with the views of Ranson[18] who showed that the mortality rate in acute pancreatitis diminishes when biliary surgery is postponed. In the case of impacted stones, the best approach now appears to be endoscopic retrograde sphincterotomy[19].

In 97 per cent of our patients retroperitoneal infection was present. Infection was diagnosed successfully by percutaneous aspiration in the ten patients on whom it was performed. The high frequency of infection in our series is probably due to the timing of surgery. Warshaw and Gongliang[16] have shown that pancreatic abscess usually appears 2–3 weeks after the onset of the disease. In a retrospective autopsy study, Renner *et al.* showed that in patients surviving more than 7 days, infection was present in 80 per cent of cases[4]. The high rate of infected necrosis may explain the overall mortality rate of 33 per cent that we observed, as infected necrosis increases the mortality rate[20]. It is, however, noteworthy that the mortality rate was 18·2 per cent in the patients operated on primarily by a limited incision. We conclude that surgical treatment of severe acute pancreatitis through a direct retroperitoneal approach is a relatively safe and simple method of removing necrosis and infected fluid collections.

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Contrast-enhanced abdominal computed tomography scanning and prediction of severity of acute pancreatitis: a prospective study

One hundred and fifty-two patients were admitted to a single hospital with a diagnosis of acute pancreatitis during a 31-month period. Of these, 126 patients had contrast-enhanced abdominal computed tomography (CT) scans within 72 h of admission; 92 of these attacks were clinically mild, 34 were clinically severe. A single consultant radiologist reported the scans 'blind' and noted whether pancreatic enhancement was normal, increased or decreased, and whether there was loss of peripancreatic tissue planes. The maximum anteroposterior measurement of the pancreatic head and body were multiplied together to produce a 'pancreatic size index' (cm^2). Significantly more patients with severe attacks had decreased pancreatic enhancement (79 versus *58 per cent,* $P = 0{\cdot}01$*) and loss of peripancreatic tissue planes (82* versus *54 per cent,* $P = 0{\cdot}006$*). The median (range) pancreatic size index for clinically severe attacks was 12·8* cm^2 *(3·0–52·5), and for mild attacks was 6·0* cm^2 *(1·1–23·4),* $P < 0{\cdot}0001$*. Modified Glasgow criteria had a sensitivity of 85 per cent and specificity of 79 per cent for clinically severe attacks. A pancreatic size index of* $\geqslant 10$ cm^2 *had a sensitivity of 71 per cent and specificity of 77 per cent for clinically severe attacks. In conclusion, although there were highly significant differences between the clinically severe and mild groups with respect to pancreatic enhancement, peripancreatic tissue planes and pancreatic size indices, these CT criteria did not improve on modified Glasgow criteria for prediction of disease severity.*

Keywords: Acute pancreatitis, contrast-enhanced computed tomography, disease severity, prognosis

N. J. M. London,
J. P. Neoptolemos,
J. Lavelle*, I. Bailey and
D. James*

Departments of Surgery and
**Radiology, Clinical Sciences*
Building, Leicester Royal Infirmary,
PO Box 65, Leicester LE2 7LX, UK
Correspondence to:
Mr N J M. London

The mortality rate of acute pancreatitis in the UK is about 10 per cent[1-4]. The ability to predict those patients whose pancreatitis is going to follow a severe course allows selective intensive therapy and, in the case of gallstone pancreatitis, a reduction in morbidity and mortality rate by endoscopic sphincterotomy[5]. The methods used to predict severity have included clinical judgement[6], single[7] or multiple[8] biochemical criteria, and peritoneal fluid analysis[9]. Although it has been demonstrated that abdominal computed tomography (CT) scanning is valuable in the diagnosis of pancreatitis[10] and its local complications such as pancreatic necrosis[11,12], abscess[13,14] and pseudocyst[15], there have been few prospective studies[16-22] concerning the prediction of severity by abdominal CT. Those studies that have been performed have examined selected patients, not all of whom have been scanned early in the course of their disease. The CT criteria have been complex and no studies have produced sensitivities and specificities of these criteria for severe attacks.

The purpose of this prospective study was to obtain an abdominal contrast-enhanced CT scan within 72 h of admission on all patients with acute pancreatitis and, having determined the CT criteria that best predicted the clinical severity of the disease, to compare them with an established clinicobiochemical prognostic system.

Patients and methods

During the period May 1984–December 1986 patients admitted to the Leicester Royal Infirmary with acute pancreatitis were referred for contrast-enhanced CT scanning. The diagnosis was based on a serum amylase > 1000 units/l (Phadebas method) in the presence of a compatible clinical picture. The predicted severity of the attack was determined within 48 h using eight of the Glasgow criteria, including age > 55 years but excluding a serum alanine transaminase > 200 units/l[23] (*Table 1*).

All scans were performed within 72 h of admission on a GE 8800 scanner (General Electric, Milwaukee, USA) and reported 'blind' by a single consultant radiologist. A plain scan was followed by a contrast-enhanced scan taking 10 mm contiguous cuts during an intravenous infusion of 100 ml Niopam 370 (Merck, Alton, UK). Pancreatic enhancement was defined as increased, normal or decreased, relative to the enhancement of the liver and spleen. It was noted whether there was loss of peripancreatic tissue planes, and the maximum anteroposterior measurements (in centimetres) of the pancreatic head, body and tail were recorded. These measurements were taken opposite the right-hand border of the lumbar vertebrae, the left-hand border of the aorta and the left renal hilum respectively. The measurements from 50 scans were repeated by an independent observer in order to determine their reproducibility. A clinically severe outcome from pancreatitis was defined as death or a major local or systemic complication. The different

Table 1 *Criteria used to predict severity of attack within 48 h of admission (modified Glasgow criteria)*

Age > 55 years	Arterial $PO_2 < 8{\cdot}0$ kPa
White cell count $> 15 \times 10^9$/l	Albumin < 32 g/l
Blood glucose > 10 mmol/l*	Calcium < 2·0 mmol/l
Urea > 16 mmol/l	Lactate dehydrogenase > 600 units/l

* Patients with diabetes mellitus not included. Predicted mild, 0–2 factors, predicted severe, 3–8 factors

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Table 2 *Clinical severity of 152 patients who were and were not scanned during the study period*

	Scanned ($n=126$)	Not scanned ($n=26$)
Severe attack	34* (27)	11* (42)
Mild attack	92 (73)	15 (58)
Deaths	6† (5)	7† (27)

Figures in parentheses are percentages. * Not significant, † $P<0·01$, χ^2 test

Table 3 *Details of the 126 patients who had computed tomography scans*

	Clinical severity	
	Mild ($n=92$)	Severe ($n=34$)
Median age in years (range)	59 (22–90)	65 (19–90)
Men	47 (51)	20 (59)
Women	45 (49)	14 (41)
Aetiology of pancreatitis		
Biliary	59 (64)	19 (56)
Alcohol	16 (17)	8 (24)
Other	17 (18)	7 (21)

Figures in parentheses are percentages

Table 4 *Major complications in the 34 patients with clinically severe attacks*

Complication	No of patients
Respiratory failure	11 (3)
Pancreatic abscess	6 (3)
Pancreatic pseudocyst	5
Pneumonia	5
Renal failure	4
Pseudo-obstruction	1
Duodenal obstruction	1
Disseminated intrasvacular coagulation	1

Numbers in parentheses indicate deaths

CT parameters and the modified Glasgow criteria were compared with respect to their ability to predict the clinical outcome

Statistical analysis

Continuous variables were analysed by the two-tailed Mann–Whitney U test. Discrete variables were analysed by the χ^2 test with Yates' correction when the expected number of observations was small. Statistical significance was assumed to be $P<0·05$ Sensitivity and specificity were calculated as described by McNeil *et al* [24]

Results

During the period of the study, 152 patients were admitted to the Leicester Royal Infirmary with a diagnosis of acute pancreatitis. Of these, 126 patients (83 per cent) had abdominal contrast-enhanced CT scans within 72 h of admission and 26 patients (17 per cent) were not scanned. The clinical severity of those patients who were and were not scanned is given in *Table 2*. The age and sex of the 126 patients who had CT scans and the aetiology of their attacks is given in *Table 3*. None of these 126 patients was subsequently found to have a diagnosis other than that of acute pancreatitis. The major complications of those patients with clinically severe attacks are given in *Table 4*. There were six deaths, and nine patients (7 per cent) required operations for local complications of pancreatitis.

The differences between the clinically mild and severe groups with respect to pancreatic enhancement, peripancreatic tissue planes and pancreatic size measurements are given in *Tables 5* and *6*. When 50 pancreatic size measurements were repeated by a second observer the median (range) difference between his measurements and those of the original radiologist was 0·5 cm (0·0–1·4) ($P=0·8$, Wilcoxon matched-pairs signed-ranks test).

The product of the pancreatic head and body measurements (which we called the 'pancreatic size index') provided the best sensitivity and specificity for clinically severe attacks. The sensitivities and specificities of various CT criteria, modified Glasgow criteria, and a combination of the two for severe attacks are given in *Table 7*. There were 11 patients who developed local complications of their pancreatitis (six pancreatic abscesses, five pseudocysts); *Table 8* compares the CT findings in these 11 patients with the findings in the 115 patients who did not develop local complications. A pancreatic size index of $\geq 10\,\text{cm}^2$ had a sensitivity of 73 per cent (8/11 patients) and specificity of 68 per cent (78/115 patients) for predicting the development of local complications.

Discussion

This is the first report from the UK of abdominal enhanced CT and the prediction of severity in acute pancreatitis. Previous studies from the USA[19–21], FRG[16–18] and Switzerland[22] have

Table 5 *Comparison of pancreatic enhancement and peripancreatic tissue planes in clinically mild and severe groups*

	Clinical severity	
	Severe ($n=34$)	Mild ($n=92$)
Pancreatic enhancement		
Decreased	27* (79)	53* (58)
Normal	7 (21)	39 (42)
Peripancreatic tissue planes		
Lost	28† (82)	50† (54)
Normal	6 (18)	42 (46)

Figures in parentheses are percentages * $P=0·01$, χ^2 test, † $P=0·006$, χ^2 test

Table 6 *Pancreatic size measurements in clinically severe and mild groups*

	Clinical severity		
Pancreatic size measurement (cm)	Severe ($n=34$)	Mild ($n=92$)	P
Pancreatic head (H)	4·0 (2·0–7·5)	3·0 (1·1–6·0)	0·0001
Pancreatic body (B)	3·0 (1·5–7·0)	2·0 (1·0–4·0)	0·0001
Pancreatic tail (T)	2·8 (1·5–5·0)	2·0 (1·0–7·0)	0·0200
$(H \times B)$ (cm^2)	12·8 (3·0–52·5)	6·0 (1·1–23·4)	0·0001
$(H \times T)$ (cm^2)	10·1 (3·0–37·5)	6·0 (1·1–21·0)	0·0002
$(B \times T)$ (cm^2)	8·5 (2·3–35·0)	4·9 (1·0–21·0)	0·0007
$(H \times B \times T)$ (cm^3)	34·8 (4·5–262·5)	15·0 (1·1–80·0)	0·0001

Values are median (range) in cm, P value by Mann–Whitney U test

Table 7 *Sensitivities and specificities of computed tomography criteria, modified Glasgow criteria, and a combination of the two for predicting clinically severe attacks*

Criterion	Sensitivity (%)	Specificity (%)
Decreased pancreatic enhancement	79	42
Loss of peripancreatic tissue planes	82	45
$(H \times B) \geq 10\,\text{cm}^2$	71*	77
Modified Glasgow criteria (MGC)	85*	79
MGC plus $(H \times B) \geq 10\,\text{cm}^2$	56	97
MGC and/or $(H \times B) \geq 10\,\text{cm}^2$	100	58

H, diameter of pancreatic head, B, diameter of pancreatic body, $(H \times B)$ cm^2 = pancreatic size index * Not significant, χ^2 test

Table 8 *Comparison of computed tomography (CT) findings in patients who developed local complications of their pancreatitis and those who did not*

CT finding	Local complications ($n=11$)	No local complications ($n=115$)	*P* value
Pancreatic size index (cm^2) (median value)	13·5	6·3	0·002*
Number of patients with			
Decreased pancreatic enhancement	9 (82)	71 (62)	0·070†
Loss of peripancreatic tissue planes	9 (82)	70 (61)	0·063†
Pancreatic size index $\geqslant 10\,cm^2$	8 (73)	37 (32)	0·02†

Figures in parentheses are percentages. * *P* value by Mann–Whitney *U* test; † *P* value by χ^2 test

examined selected patients; the high incidence of alcoholic pancreatitis in the USA[25,26] makes it difficult to relate the results of studies performed there to the situation in the UK. Although a recent prospective study from Geneva[22] has scanned a population with a similar incidence of gallstone pancreatitis (55 per cent) to that seen in the UK (44–57 per cent)[4,8,23,27] the incidence of pancreatic abscess (17·6 per cent) suggested 'that a relatively high proportion of severe pancreatitis' was included. The age–sex distribution, aetiology of pancreatitis, mortality rate (5 per cent), incidence of clinically apparent pseudocyst (4 per cent) and abscess (5 per cent) in our study were similar to those of other studies of pancreatitis in the UK, confirming that the patients in this study were not selected. The proportions of patients with severe attacks amongst those who had and did not have CT scans were not significantly different, indicating that the patients who were scanned had not been selected in terms of severity. There were inevitably significantly more deaths amongst the group of patients who were not scanned because those who were moribund on admission were not referred for CT scanning.

Eighty-three per cent of patients admitted with acute pancreatitis during the study period had abdominal enhanced CT scans within 72 h of admission. Although it would have been preferable to scan all patients within 24 h of admission, this was not possible because we were unable to scan patients during the weekend period. It is important to scan patients early in the course of their disease not only because selective intensive therapy can then be implemented at an early stage but also because it has been shown that the concordance between CT findings and clinical staging increases from 71 per cent at 72 h to 85 per cent at 6 days[28] This means that CT criteria derived from scans performed after 72 h will inevitably produce high sensitivities and specificities for severe attacks since the local disease process is well established by this time.

The design of this study was prospective and the CT criteria were chosen before the study commenced. The only retrospective analysis was the derivation of the 'pancreatic size index' which best predicted severity The value of this pancreatic size index for the prediction of severity does therefore need to be confirmed in a prospective study. We chose relatively simple CT criteria because we felt that a complex grading system would not be applicable to general surgical practice.

It has been demonstrated both experimentally[29,30] and in patients with alcohol-induced pancreatitis[31,32] that there is reduced contrast enhancement of the pancreas in those cases that develop severe attacks. We assessed pancreatic enhancement visually because we wished to estimate overall pancreatic enhancement rather than the mean value of selected areas as measured by Houndsfield units[30]. Similarly it has been reported that extrapancreatic spread of oedema or 'phlegmon' correlates with morbidity and mortality rates from acute pancreatitis[16–18,20–22,33–35]. Extrapancreatic fluid collections are prone to secondary bacterial infection and are recognized CT risk factors for the development of pancreatic abscess[13,21]. These fluid collections have not been shown to correlate with overall prognosis[14,16,36] and we did not include them in our CT criteria. The measurement of extrapancreatic oedema has been complex in previous studies[17,18,22]. We simplified the interpretation of the CT scans by recording whether or not there was loss of peripancreatic tissue planes[37].

At the time that this study commenced there were no reports of the prognostic significance of the degree of pancreatic parenchymal swelling. Becker *et al* [18] and Takada *et al.*[37] have since shown that the degree of pancreatic swelling is correlated with clinical severity. Whereas Becker *et al.*[18] recorded pancreatic size by comparing the sagittal diameter of the pancreas with that of the adjacent vertebral body, we used measurements of pancreatic head, body and tail taken from the CT scans.

Although there were significantly more patients with severe pancreatitis who had loss of peripancreatic tissue planes and decreased pancreatic enhancement, the specificity of these criteria for severe attacks was too low to be of clinical value (*Table* 7). These findings are similar to those of Grabbe *et al* [16]. The differences in pancreatic size measurements between the mild and severe groups were highly significant. The CT size index which best predicted the severity of pancreatitis was the product of the head and body measurements, or 'pancreatic size index'. A pancreatic size index $\geqslant 10\,cm^2$ had a sensitivity of 71 per cent and specificity of 77 per cent for severe attacks (*Table* 7). This compared with a sensitivity of 85 per cent and specificity of 79 per cent using modified Glasgow criteria. The combination of a pancreatic size index $\geqslant 10\,cm^2$ and/or modified Glasgow criteria produced a sensitivity or specificity which was too low to be of any clinical value (*Table* 7).

It has been suggested by Ranson *et al.*[13] that early imaging of the pancreas by CT can identify a group of patients with an increased risk of pancreatic abscess. Vernacchia *et al.*[14] have not been able to reproduce Ranson's results and have suggested that CT should be restricted to patients who have a clinically suspected surgical complication. We have found that although CT is sensitive (73 per cent) for the prediction of the development of local complications, the specificity is too low (68 per cent) to be of any clinical value. We would stress that the purpose of this study was to determine the value of an early contrast-enhanced CT scan for the prediction of overall clinical severity. Our results are not comparable to those of Block *et al.*[11] and Kivisaari *et al* [12] who have used high-dose, rapid-bolus intravenous contrast infusions in conjunction with dynamic CT scanning in order to detect pancreatic necrosis in patients with established severe pancreatitis

It is difficult to make meaningful comparisons between the results of this study and those of other prospective studies because previous reports have examined patients with a different spectrum of disease to that seen in the UK (*Table* 9). We would, however, agree with Grabbe *et al* [16] that a contrast-enhanced scan does not improve on the prognostic value of a plain scan We have also noted that in certain cases the CT prediction of severity may be markedly different from the clinical course of the disease[16,19,22]. We found that the sensitivities and specificities of CT criteria for the prediction of severe pancreatitis were similar to those of modified Glasgow criteria and for economic reasons we would not recommend routine CT scanning of all patients with acute pancreatitis. It has been suggested that CT should be reserved for patients who demonstrate persistent toxicity[13], or restricted to those who are predicted severe by multiple biochemical criteria[22,38–40]. It has yet to be determined whether or not these policies will reduce the morbidity or mortality of patients with established or biochemical predicted severe attacks It has, however, been shown that abdominal CT, with contrast enhancement[11], is valuable in the assessment of established local complications of acute pancreatitis[41–43] and that it is superior to ultrasonography in this situation[10].

In conclusion, although it has been shown by other authors that contrast-enhanced CT is valuable in the diagnosis and

Table 9 *Details of prospective studies of computed tomography scanning and prediction of severity in acute pancreatitis*

	Hill *et al.*[19] (1982)	Grabbe *et al.*[16] (1982)	Becker *et al.*[18] (1985)	Balthazar *et al*[21] (1985)	Nordestgaard *et al.*[20] (1986)	Kursawe *et al*[17] (1987)	Clavien *et al*[22] (1988)	London *et al* † (1989)
Number of patients	91	59	92	83	51	230	176	126
Timing of scans	<48 h	<48 h	<24 h	1–10 days	1–7 days	'variable'	<36 h	<72 h
Biliary aetiology (%)	2	NG	NG	13	27	NG	55	62
Severe attacks (%)	NG	52	55	33	35	72	34	27
Abscess rate (%)	3	NG	NG	22	8	NG	18	5
Mortality rate (%)	NG	23	20	7	8	NG	12	5
Operation rate* (%)	NG	NG	37	23	20	39	20	7

NG, Not given, * operation rate refers to operations for local complications of pancreatitis; † the present study

management of the local complications of acute pancreatitis, we would not recommend routine CT scanning of all patients with the disease.

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Case report

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Superior mesenteric vein thrombosis caused by Yersinia pseudotuberculosis

R. C. Stuart, A. L. Leahy, M. T. Cafferkey* and R. B. Stephens

*Departments of Surgery and *Microbiology, St James's Hospital, St. James's Street, Dublin 8, Ireland*

Correspondence to. Mr R B Stephens

Since the first isolation of *Yersinia pseudotuberculosis* from the mesenteric lymph node of a patient who had the clinical picture of acute appendicitis[1] many reports of mesenteric lymphadenitis secondary to *Y. pseudotuberculosis* have appeared. *Y pseudotuberculosis* may also cause intestinal ulceration, peritonitis and septicaemia, sometimes with a fatal outcome.

We report a case of massive mesenteric lymphadenitis caused by *Y. pseudotuberculosis*, resulting in superior mesenteric vein thrombosis and small intestinal gangrene.

Case report

A previously healthy 39-year-old man presented with a 1-week history of crampy central abdominal pain, watery diarrhoea and vomiting. On examination he was ill, febrile, and his abdomen was distended and tender to deep palpation Other findings, including rectal examination, were normal. Initial investigations revealed a neutrophil leucocytosis

On the evening of admission laparotomy was performed The entire mesentery was thickened with massive lymph node enlargement. Of the necrotic small intestine 6 cm were resected, commencing at the ligament of Treitz. The patient was anticoagulated with intravenous heparin for 5 days followed by oral warfarin for 3 months. Improvement was rapid, and he was discharged 14 days after surgery Some 5 years later the patient remains well with no recurrence or progression to inflammatory bowel disease.

Histological examination revealed transmural necrosis and marked congestion There was extensive venous thrombosis and the vessels in the area of necrosis demonstrated prominent acute mural inflammation secondary to ischaemia rather than to a primary vasculitis. The lymph nodes were reactive and congested with no evidence of lymphoma or malignant histiocytosis

Y. enterocolitica and Y pseudotuberculosis serology were performed Antibody to *Y pseudotuberculosis* was present at a titre of 640. After absorption with *Salmonella enteritidis* the residual *Y pseudotuberculosis* titre was 160 This was considered as evidence of infection with *Y pseudotuberculosis* as the upper limit of the normal range is a titre of 80 At 6 weeks follow-up the *Y pseudotuberculosis* titre (absorbed) was 80

Discussion

Two basic forms of the *Y. pseudotuberculosis* infection have been described: an often fatal septicaemia and a more benign mesenteric lymphadenitis[2]. The benign mesenteric lymphadenitis is self-limiting, is not associated with underlying diseases and resolves without antibiotic intervention Systemic yersinosis requires antibiotic therapy and is associated with underlying illness such as chronic liver disease, siderosis, and the administration of desferrioxamine.

Life-threatening complications of mesenteric lymphadenitis are rare. Venous thrombosis caused by *Y pseudotuberculosis* has not been previously reported. One case of small bowel gangrene caused by *Y. enterocolitica III* has been cited[3]. The mechanism of the venous thrombosis remains unproved. The histological pattern of the vessels in our case and that of Leino *et al.*[3] was secondary to ischaemia rather than a primary vasculitis. The most likely cause of the obstruction of the superior mesenteric vessels was extraluminal compression by the massive lymphadenopathy

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Proctocolectomy and ileoanal pouch anastomosis without conservation of a rectal muscular cuff

The technique of proctocolectomy and formation of an ileal reservoir with ileoanal anastomosis is well described. It is believed that the conservation of a rectal muscular cuff is necessary for continence but no data are available to support this contention. The aims of this study were to describe the clinical and physiological aspects of continence after proctocolectomy and ileal J pouch anastomosis without conservation of a rectal muscular cuff. Eighteen consecutive patients (mean age 37·3 years, 16 ulcerative colitis, two familial polyposis) who underwent proctocolectomy and ileoanal anastomosis on the dentate line were studied 6 months after closure of the loop ileostomy. The 18 patients and eight controls underwent: (a) anal manometry; (b) determination of maximum tolerable volume (MTV); (c) liquid continence test (infusion of NaCl at 60 ml/min for 25 min) with simultaneous measurement of ileal reservoir pressure. The volume evacuated during 5 min after the continence test was also measured. The frequency of bowel actions was (mean ± s.e.m.) 5·3 ± 0·4 per 24 h (nocturnal 1·14 ± 0·26). Seventeen of 18 patients (94 per cent) had normal continence and defaecation; one patient was incontinent. A decrease in resting anal canal pressure (102·5 ± 4 versus *47·5 ± 6 cmH_2O) was observed after ileoanal anastomosis. A rectoanal inhibitory reflex was elicited in one of the 18 patients (6 per cent). Patients were able to retain 1023 ± 68 ml saline during the liquid continence test. The percentage evacuation of the ileal reservoir was 61 ± 4·5 per cent. Correlations were found* ($P = 0{\cdot}05$) *between daily stool frequency and the volume of saline retained during the liquid continence test. It is concluded that conservation of a rectal muscular cuff is not necessary for the achievement of good clinical results.*

Keywords: Ileoanal anastomosis, ileal pouch, proctectomy, continence, ulcerative colitis

S. Chaussade,
A. Verduron,
M. Hautefeuille*,
G. Risleight, J. Guerre,
D. Couturier, P. Valleur†
and P. Hautefeuille†

*Hôpital Cochin, *Hôpital Saint Lazare and †Hôpital Lariboisiere, Paris, France*

Correspondence to:
Dr S. Chaussade, Service du Pr Guerre, Hôpital Cochin, 27 rue du Fg St Jacques, 75674 Paris-Cedex 14, France

Proctocolectomy with ileal pouch–anal anastomosis for the treatment of chronic ulcerative colitis and familial polyposis coli offers an alternative to conventional ileostomy or ileorectal anastomosis[1].

All the surgical techniques proposed in the past have been based on the theoretical assumption that the last 2 or 3 cm of rectal muscular cuff are essential for the maintenance of adequate anal continence, but no data are available to support this concept. More recently, proctocolectomy with total removal of the rectum followed by ileal pouch anastomosis to the dentate line has been described[2–5]. The aim of this study was to determine: (a) the anal and the ileal reservoir function after colectomy, total removal of the rectum and ileal pouch anastomosis; and (b) which functional features of the anal sphincter and ileal pouch are responsible for poor or good clinical results.

Patients and methods

Patients

Eighteen consecutive patients who had undergone proctocolectomy with ileal pouch–anal anastomosis for chronic ulcerative colitis ($n = 16$) or familial polyposis coli ($n = 2$) were studied. The group consisted of eight men and ten women aged from 21 to 73 years (mean ± s.e.m., 37·3 ± 2·6 years). All medication was stopped for at least 4 days before the study.

Operative technique

The surgical procedure consisted of an excision of the colon followed by a close perimuscular dissection of the rectum down to the pelvic floor. The rectum was transected a few centimetres above the anorectal junction and the rectal stump was everted through the anus. This rectal stump was transected at the level of the dentate line and an ileoanal anastomosis was performed manually under direct vision as previously described for coloanal anastomosis[6]. The 18 patients had a J ileal pouch constructed. In each patient, the ileoanal anastomosis was protected by means of a defunctioning ileostomy which was closed 8–12 weeks later.

Clinical test

The frequency of bowel movements was recorded on a diary card for 7 days before the study; no special diet was given.

Anal sphincter studies

Anal manometry (1). Pressure recordings were made with a probe made of three latex balloons tied to polyethylene tubes and connected to pressure transducers[7]. The balloon at the tip of the probe was used to distend the rectum. The second and third balloons (10 mm apart) were filled with water and placed in the upper and lower anal canal respectively. The probe was introduced so that the distal tip of the lowest balloon remained just at the anal margin. From 10 to 100 ml of air was injected into the rectal balloon for 1 min to elicit a rectoanal inhibitory reflex which was recorded in the upper part of the anal canal. Each distension was separated by a 1-min period.

Anal manometry (2). Radial pressures in the anal canal were measured using a rigid probe featuring four perfused channels (internal diameter 0·8 mm) with side-ports 90° apart[8]. A latex balloon was located at the tip of the probe (7 × 1·5 cm) to measure pouch capacity. The four channels were perfused with water (0·5 ml/min) using a low compliance pneumohydraulic system with pressure transmitted to water-filled strain gauges (Gould, Statham P. 23, California, USA)) and permanently recorded on a Beckmann R511 recorder (Sensormedic, Gayny, France).

After the pouch was evacuated the patient adopted the left lateral position. The probe was passed transanally to about 6 cm, just above the puborectalis, and the side-ports were positioned to permit simultaneous recording from the anterior, posterior, right lateral and left lateral quadrants. The probe was withdrawn in 0·5 cm stages every 2 min,

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Table 1 *Results of manometric investigations*

	Ileoanal anastomosis ($n=18$)	Control ($n=8$)	P
Resting pressure (cmH$_2$O)	47·5 ± 6·0	102·5 ± 4·0	$P<0.01$
Squeeze contraction (cmH$_2$O)	136·3 ± 10·0	135·6 ± 11·0	n.s.
Sphincter length (cm)	2·95 ± 0·12	2·9 ± 0·17	n.s.
Volume at first sensation (ml)	60·0 ± 14·5	12·5 ± 1·5	$P<0.05$
Maximum tolerable volume (ml)	270 ± 23	245 ± 22	n.s.

Values are mean ± s.e.m., n.s., not significant

Table 2 *Anal sphincter pressures recorded with water-filled balloons*

	Ileoanal anastomosis ($n=18$)	Control ($n=7$)	P
Upper anal canal pressure (cmH$_2$O)	35·0 ± 6·0	84·0 ± 3·5	$P<0.05$
Lower anal canal pressure (cmH$_2$O)	46·5 ± 3·9	42·5 ± 7·0	n.s.
Squeeze contraction (45 s)	117·0 ± 12·5	115·0 ± 19·0	n.s.
Inhibitory rectoanal reflex	1 (5·5%)	7 (100%)	$P<0.05$

Values are mean ± s.e.m., n.s., not significant

recording the resting pressures within the anal canal at each level as described by Taylor *et al.*[8]. The probe was then reinserted and the procedure repeated, this time asking the patient to squeeze maximally on the probe for 15 s at each position. At the end of this study, the probe was reinserted at the upper part of the high pressure zone. The bag was inflated with 20-ml increments of air at 20-s intervals, and the sensation threshold volume and maximum tolerable volume (MTV) were measured[9]. Results from this study were compared with those obtained from eight healthy volunteers (five men, three women; mean age 32 ± 3 years).

Saline retention test

Assessment of the anal sphincter stressed in a standard manner was accomplished by inserting a polyvinyl probe (outside diameter 7 mm) into the ileal reservoir until its tip was approximately 9 cm from the anal margin. The probe used for this test had two catheters: one to infuse the saline solution[10] through the tip of the probe and another to record intraluminal pressures during the saline test. The latter catheter (internal diameter 1 mm) was perfused with water (0·5 ml/min) and was located 3 cm from the tip of the probe. While subjects sat on a portable commode with a special volumetric collection vessel, 150 mM NaCl was infused at 60 ml/min for 25 min. The saline continence test was interrupted when the first leakage (>10 ml) appeared, when the subject complained of a sustained feeling of nausea or pelvic discomfort, or when 1500 ml had been infused. The MTV and the volume of the first contraction appearing in the ileal pouch were also measured. At the end of the saline continence test the patients were asked to evacuate the pouch contents as completely as possible over a period of 5 min. The evacuated volume of saline was measured and the efficiency of pouch evacuation was represented by the ratio of the evacuated volume divided by the MTV during the saline test.

Statistical analysis

The results were evaluated using the Mann–Whitney *U* test for unpaired data, P values <0.05 were taken to be statistically significant. Correlation of test results to functional results was carried out by linear regression analysis.

Results

Clinical findings

Stool frequencies (mean ± s.e.m.) at home were 5·3 ± 0·4 per 24 h (range 3–9). During the night this frequency varied from 0 to 3·5 per 24 h (mean ± s.e.m., 1·14 ± 0·26). One patient was incontinent. Seventeen patients were continent and able to defaecate spontaneously; three wore a pad, mostly at night. Nine patients had soiling, mostly during the night. Stool weight varied from 79 to 959 g (mean ± s.e.m., 384 ± 53).

Anal manometry (1)

The length of the pressure zone in patients following ileal pouch anastomosis (mean ± s.e.m., 2·95 ± 0·12 cm) was not significantly different from that of the control population (2·9 ± 0·17 cm, $P>0.05$). The resting anal canal pressure in patients (47·5 ± 6·0 cmH$_2$O) was significantly lower than in the control group (102·5 ± 4·0 cmH$_2$O, $P<0.01$). The squeeze pressures were similar between the two groups (patients, 136·3 ± 10·0 cmH$_2$O; controls, 135·6 ± 11·0 cmH$_2$O, $P>0.05$) (*Table 1*).

Anal manometry (2)

The pressures at the upper part of the anal canal were significantly lower (*Table 2*) in the patients than in the controls. However, the pressure at the lower part of the anal canal and the squeeze contractions did not differ between patients and controls.

The rectoanal inhibitory reflex was elicited in all controls when the latex rectal balloon was distended with small amounts of air (mean threshold 12·5 ml, range 10–20). In contrast, the reflex could be elicited in only one patient despite distension of the balloon up to 100 ml of air. Nevertheless, 16 of the 17 patients with an absent rectoanal inhibitory reflex had normal continence.

Function of ileal pouch

The volume at which sensation threshold was reached was significantly higher in the ileoanal anastomosis group (mean ± s.e.m., 60 ± 14·5 ml) than in controls (12·5 ± 1·5 ml, $P<0.05$).

The MTV or pouch capacity as determined by incremental inflation of a latex bag was 270 ± 23 ml in ileoanal pouch patients, which was not significantly different from the MTV of heathy volunteers (245 ± 22 ml).

Saline retention test

Patients were able to retain 1023 ± 68 ml (mean ± s.e.m.) saline administered at a rate of 60 ml/min (*Table 3*). The volume at which the first contraction in the ileal reservoir appeared was 346 ± 96 ml (range 62–1500 ml). The duration of the first contraction appearing in the reservoir varied from 12 to 40 s (mean ± s.e.m., 25 ± 2·9 s) while the amplitude ranged from 17 to 65 cmH$_2$O (36 ± 4·5 cmH$_2$O). The percentage of the infused saline that was evacuated ranged from 29 to 94 per cent (61·0 ± 4·6 per cent).

The patient with nocturnal faecal incontinence was the oldest patient of this study (aged 73 years). Her resting anal pressure (14 cmH$_2$O) and squeeze contraction (75 cmH$_2$O) were low.

There was no correlation between stool frequency and the following parameters: MTV, anal pressures, percentage evacuation of the infused saline, and the volume at which contraction appeared in the ileal reservoir during the saline continence test. There was, however, a correlation between stool frequency and the maximum retained volume of saline during the saline retention test ($P=0.05$). The anal resting pressure did not differ significantly between the patients with and those without soiling. Nevertheless, five out of nine patients with soiling had a low (<30 cmH$_2$O) resting anal pressure, only one of the nine patients without soiling had a low resting pressure.

Discussion

The technique of ileoanal anastomosis for the treatment of ulcerative colitis and familial polyposis is well documented. At

Table 3 *Results of the saline retention test in patients with ileoanal anastomosis*

Maximum retained volume (ml)	1023 ± 68 (614–1500)
Volume leading to first contraction (ml)	346 ± 96 (62–1500)
Percentage evacuated in 5 min	61·0 ± 4·6 (29–94)

Values are mean ± s.e.m., with range in parentheses the present time attention is focused on the type and size of the reservoir and the conservation of a rectal cuff. The conservation of a rectal muscle necessitated a mucosectomy and it has recently been demonstrated[11] that fragments of rectal mucosa can remain between the pouch and the rectal cuff with the potential risk of recurrence of the disease or carcinogenicity.

Our work shows that conservation of a rectal muscular cuff is not essential in order to obtain good functional results; the daily stool frequency is comparable to that reported by Metcalf *et al* [1]. At 12 months, stool frequency was similar (5·3 ± 0 45 during the daytime). By contrast, during the night, stool frequency decreased from 1 14 ± 0·26 to 0·84 ± 0·24, suggesting adaptation of the ileal reservoir Total resection of the rectum with the pouch anastomosis on the dentate line renders mucosectomy unnecessary and permits removal of the entire rectal mucosa.

It has been proposed that conservation of the rectal muscular cuff is necessary to obtain good clinical results and to ensure a postoperative rectoanal inhibitory reflex. Stryker *et al* [12], conserving the cuff, found that a rectoanal inhibitory reflex was present in only 5 per cent of patients This demonstrated that there may be no relationship between the presence of the reflex and conservation of the rectal cuff. The prerequisite for normal continence is the conservation of mucosa located between the dentate line and the anal margin since numerous nerves endings are situated at this level[13] Furthermore, as proposed by Johnston *et al.*[5], it could be important to perform the anastomosis a few millimetres above the dentate line.

Low anal resting pressure was found in our study, and it was due to a decrease at the upper level of the anal sphincter. This decrease has been observed in other studies[5,14,15] where a rectal cuff was preserved and could be attributed to the surgical technique employed. The surgical technique that we adopted combined the total resection of the rectum, the eversion of the rectal stump, and an anastomosis under direct vision. In our patients the decreased anal pressure might be attributable to the dilatation or eversion of the rectal stump during surgery However O'Connell *et al.*[16] recently showed that the anal resting pressure was not significantly different with or without eversion of rectal stump. There was, in our series, no correlation between resting anal pressure, stool frequencies and the occurrence of soiling. However, low anal pressures ($<30\,\mathrm{cmH_2O}$) were more frequent in patients with soiling[16]. It has not been possible to compare anal function before and after ileoanal anastomosis because 14 out of 18 patients were operated on as emergencies.

Recently Johnston *et al.*[5] suggested that the decrease in anal resting pressure was more important when a mucosectomy was performed. In our study, the maximum anal resting pressure ($47{\cdot}5\,\mathrm{cmH_2O}$) was lower than in Johnston's patients with end-to-end anastomosis ($70\,\mathrm{cmH_2O}$) but higher than in patients with mucosal proctectomy with endoanal pull-through anastomosis ($40\,\mathrm{cmH_2O}$). This result suggests that it could be important to preserve a few millimetres of mucosa above the dentate line to avoid minor faecal leakage.

The pressure at the lower level of the anal sphincter and the squeeze contraction were similar in both the patients and controls, suggesting that the striated muscle of the anus was not affected by surgery.

The volume of the ileal pouch is the second major physiological parameter to influence continence and defaecation[17]. The absence of an ileal pouch is associated with poor clinical results. We did not find any correlation between MTV and stool frequency. Other factors should therefore be examined, such as pouch compliance, maximum volume retained during the saline continence test, percentage of evacuation of the reservoir, the volume at which the first contraction appears in the reservoir, and the duration and amplitude of the ileal contractions.

The ability to retain a large volume of saline was associated with better functional results By contrast, there was no relationship between daily stool frequency and MTV, and between MTV and the retained volume of saline. Thus the volume measured during the saline continence test could allow a more precise assessment of the functional volume of the reservoir.

The percentage of evacuation of the pouch is a good measure of the efficiency of defaecation, and our results are comparable with those of O'Connell *et al.*[18] using a different technique Stryker *et al.*[12] suggested that there was a relationship between the time that elapsed between a pouch being empty and the onset of the first ileal contraction and the daily stool frequency. In our study we did not see this relationship, but the conditions under which the saline retention test was performed were not physiological as the infusion rate of NaCl was 60 ml/min.

In conclusion, during ileoanal pouch anastomosis, conservation of a muscular rectal cuff is not necessary to obtain good clinical results. The total resection of the rectum is a particularly useful procedure where mucosectomy is difficult or when the rectum is small.

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Preoperative assessment of mesorectal lymph node involvement in rectal cancer

J. Beynon,
N. J. McC. Mortensen*,
D. M. A. Foy,
J. L. Channer, H. Rigby
and J. Virjee

Departments of Surgery, Medical Physics, Pathology and Radiology, Bristol Royal Infirmary, Bristol and
**Department of Surgery, John Radcliffe Hospital, Oxford, UK*

Correspondence to.
Mr J Beynon, Department of Surgery, Southmead Hospital, Westbury on Trym, Bristol
BS10 5NB, UK

One hundred patients with rectal adenocarcinoma were examined preoperatively with rectal endosonography (ES) and 50 were also examined with computed tomography (CT). ES predicted mesorectal lymph node involvement with an accuracy of 83 per cent, sensitivity of 88 per cent, specificity of 79 per cent, positive predictive value of 78 per cent and negative predictive value of 89 per cent. CT in comparison had an accuracy of 57 per cent, sensitivity of 25 per cent, specificity of 91 per cent, positive predictive value of 75 per cent and negative predictive value of 53 per cent. No particular histological architectural feature could be identified as responsible for false positive diagnosis though nodal size was significantly larger in the true positive and false positive group when compared with the true negatives ($P<0{\cdot}001$ *and* $P<0{\cdot}01$ *respectively).*

Keywords: Endosonography, rectal cancer, computed tomography

Pararectal lymph node involvement has considerable prognostic significance in rectal cancer giving one indication of survival prospects and the risk of local recurrence. Studies with large groups of patients generally suggest that the presence of lymph node metastases greatly decreases patients' survival[1–9] There is a close relationship between lymphatic spread and the extent of local tumour invasion, tumour histology and vein invasion[8]. Furthermore, as the number of involved nodes increases, a progressive decrease in survival has been noted[9,10]. The incidence of local recurrence is also increased by the presence of involved nodes[11–14], although this may be less important than extensive tumour invasion[15,16]

The most commonly used method of assessing nodal involvement preoperatively is digital examination, and accuracy is related to clinical experience[17]. A more reliable objective method of determining the presence of involved nodes is needed to improve patient selection for conservative methods of treatment including peranal local excision, radiotherapy, cryotherapy or laser therapy. Endosonography (ES) has been shown to be an accurate method of predicting the degree of local invasion in rectal cancer[18–24]. Can it also accurately predict mesorectal nodal involvement, and how does it compare with a more established radiological technique, computed tomography (CT)?

Patients and methods

One hundred patients with a primary rectal adenocarcinoma have been examined preoperatively with rectal ES and 46 of them were also examined using CT to assess the relative merits of the two techniques in predicting nodal involvement. All the ultrasound examinations were performed and reported by one clinician using a Bruel and Kjaer 1846 scanner*, with a rotating hand held endoprobe, and 5·5 MHz (focal length (FL) 1–4 cm) or 7·0 MHz (FL 2–5 cm) transducers The endoprobe was either introduced blindly into the rectum or placed at the level of the lesion through a specially constructed rectoscope After placement in the lumen a latex balloon, which covers the transducer, was inflated with water for good ultrasonic contact

Ultrasonic prediction of involvement was based on the identification of circular or oval echo-poor lesions in the mesorectum as suggested by Tio and Tytgat[25] in their studies using upper gastrointestinal ES for the examination of oesophageal and gastric malignancies Failure to identify any such area was taken as a negative result At the same time a note was made of the differing echo patterns produced by suspicious extrarectal lesions to see whether, in retrospect, inflammatory or normal nodes could be distinguished from involved nodes just on the basis of the echo pattern.

After resection the specimens were prepared and transverse sections taken for comparison with the radiological images A detailed examination of all the mesorectal lymph nodes within 1 cm of the tumour was made and the histological architecture noted The total number and size of nodes identified, the number of involved nodes and the number of nodes showing 'reactive' changes (defined as the presence of sinusoidal or follicular dilatation, or follicular hyperplasia, or combinations thereof) were included

ES predictions of nodal involvement were compared with histopathological assessments and results analysed using a Spearman rank correlation test[26] Pathological results relating to nodal size were analysed using the Kruskal–Wallis one-way analysis of variance and the Mann–Whitney *U* test[27].

Results

Of the 100 patients studied 56 were men and 44 women and they had an age range of 36–91 years (median 67·5) Subsequently 93 were treated by either anterior resection or abdominoperineal excision. Seven patients were treated by peranal local excision and in two cases, local lymph nodes adjacent to the tumour were also excised, the patients having refused a major resection.

Endosonography

During the initial phases of this study it soon became apparent that normal nodes and most 'reactive' nodes were not imaged and that the presence of an echo-poor lesion in the pararectal tissues was usually indicative of a lymph node metastasis (*Figure 1a* and *b*) ES could not, however, differentiate between involved nodes and islands of tumour outside the wall. The smallest positive node detected had a diameter of 0·3 cm. No hyperechoic nodes were imaged. Some echo-poor nodes detected by ES did not contain any tumour when isolated and examined pathologically (*Figure 2*).

ES predicted lymph node involvement in 49 cases and lack of involvement in 46 cases. Comparison with histopathology showed that there were 38 correct positives, 41 correct negatives, 11 false positives and 5 false negatives. Correlation of ES predictions and histopathology gave a correlation coefficient of 0·67 (d.f =93, $P<0{\cdot}001$) (Spearman rank correlation)

The accuracy of prediction of lymph node involvement was 83 per cent. The sensitivity for predicting involvement was 88 per cent, specificity 79 per cent, positive predictive value 78 per cent and negative predictive value 89 per cent.

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* *The Bruel and Kjaer 1946 scanner is manufactured by Brueland Kjaer, Naerum, Denmark.*

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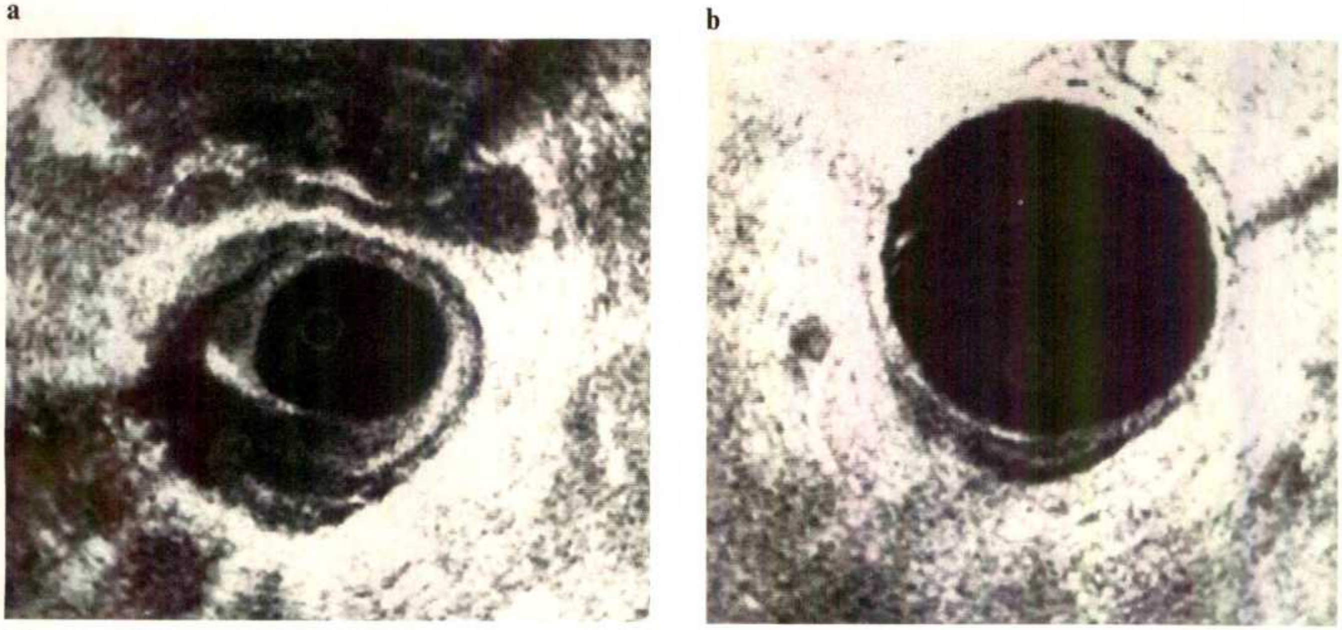

Figure 1 **a** *This ultrasound scan shows a transmural tumour (uT3) which, at this level, does not appear to have any nodal metastases;* **b** *at the upper limit of the same tumour a small echo-poor nodal metastasis was imaged in the 9 o'clock position*

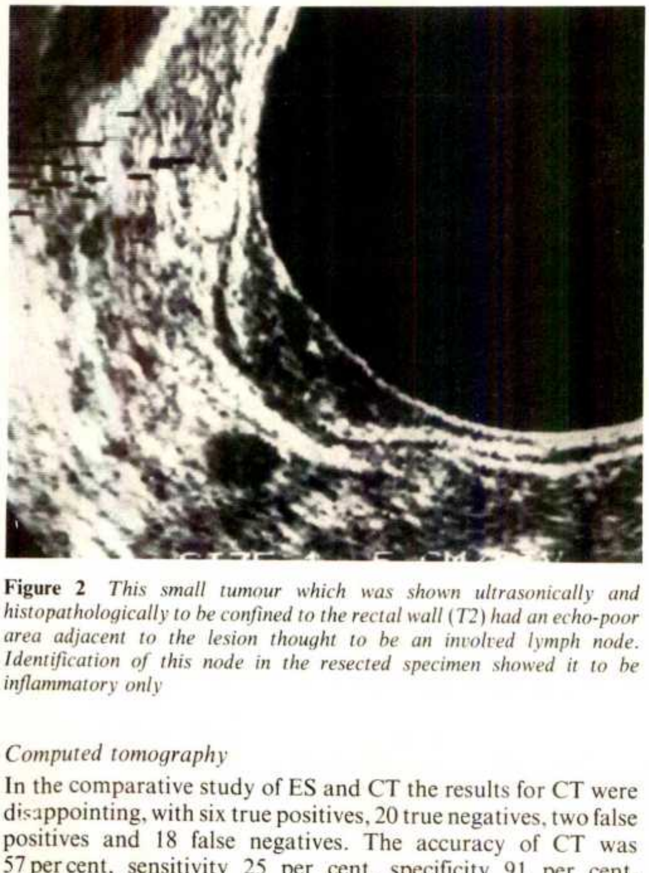

Figure 2 *This small tumour which was shown ultrasonically and histopathologically to be confined to the rectal wall (T2) had an echo-poor area adjacent to the lesion thought to be an involved lymph node. Identification of this node in the resected specimen showed it to be inflammatory only*

Computed tomography

In the comparative study of ES and CT the results for CT were disappointing, with six true positives, 20 true negatives, two false positives and 18 false negatives. The accuracy of CT was 57 per cent, sensitivity 25 per cent, specificity 91 per cent, positive predictive value 75 per cent and negative predictive value 53 per cent. The comparative results are presented in *Table 1*.

It would seem that CT can only identify large nodes (*Figure 3*) in this series identified only those larger than 1·5 cm in diameter. This ability alone is not sufficient to differentiate inflammatory from malignant nodes.

Histopathology

In 56 patients a detailed examination was performed to determine if any one histological feature or combination of features was responsible for the endosonographically false positive diagnoses. This group was chosen solely on the basis that a complete longitudinal assessment of the tumour had been made and also that there was detailed histopathological information about all nodes within 1 cm of the tumour. The results from these cases showed that there were 24 true positives, 24 true negatives, seven false positives and one false negative. All nodes were

Table 1 *The accuracy of rectal endosonography and computed tomography in predicting nodal involvement, in a series of 46 patients with adenocarcinoma of the rectum*

	Accuracy	Sensitivity	Specificity	PPV	NPV
CT	57	25	91	75	53
ES	87	92	82	85	90

CT, computed tomography; ES, endosonography; PPV, positive predictive value; NPV, negative predictive value

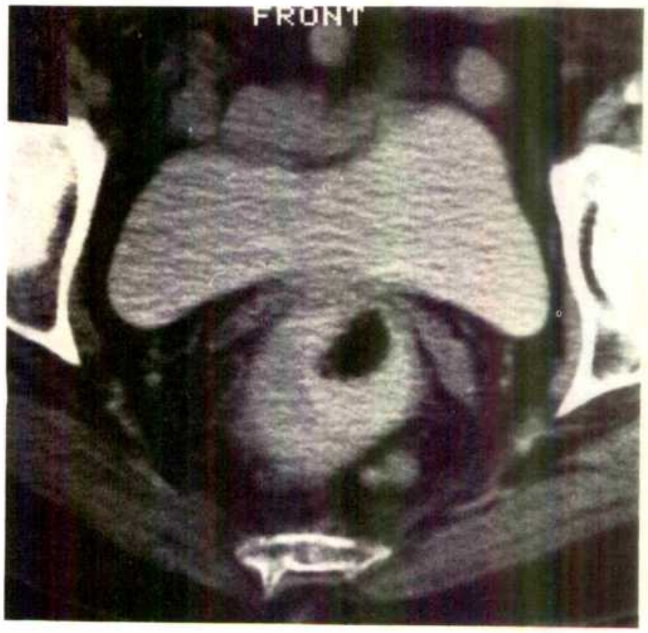

Figure 3 *This computed tomography scan demonstrates a rectal tumour with a large adjacent involved lymph node*

Table 2 *A comparison of histopathological nodal size in the endosonographically true negative, true positive and false positive groups*

Endosonographic status	Histological status	Size range (cm)	Median (cm)
Negative	Negative nodes	0·05–1·2	0·4
Positive	Positive nodes Negative nodes	0·2–1·3 0·1–0·7	0·7 0·38
Positive	Negative nodes	0·2–0·8	0·5

examined histologically for the presence of tumour metastases or the presence of 'reactive changes' as shown by the presence of sinusoidal dilatation, follicular hyperplasia, sinusoidal hyperplasia or combinations of these characteristics.

This pathological examination failed to show that any particular histological architectural feature or combination of features was responsible for the misdiagnosis of nodal involvement.

Nodal size

The histopathological size of nodes within 1 cm of the tumour was also measured in the endosonographically true positive, true negative and false positive groups to determine whether any overall difference in size existed in the lymph nodes detected in the three groups. In this analysis there were nodes from 51 resections and of these ES assessment gave 25 true negatives, 20 true positives, five false positives and one false negative. The sizes of nodes in the individual groups varied considerably (*Table 2*).

These data have been compared using the Kruskal–Wallis test for independent variables ($H = 34·96$) and subsequently using the Mann–Whitney U test. Comparison of the sizes of the histologically involved and non-involved nodes in the endosonographically 'true positive' group showed a statistically significant difference ($U = 370$, $P < 0·001$). On comparison of the histologically involved nodes in the endosonographically true positive group with the histologically negative nodes in the endosonographically false positive group no significant difference was found ($U = 264$, $P = 0·098$). In addition there was a significant difference in size between the histologically involved nodes in the endosonographically true positive group and those in the endosonographically true negative group ($U = 878$, $P < 0·001$). There was also a significant difference in histological size of nodes between the endosonographically false positive and the true negatives ($U = 350$, $P < 0·01$) (*Table 2*).

Discussion

Various methods have been used to evaluate the status of mesorectal lymph nodes before treatment. At present digital examination is the most commonly used method but it is not very accurate[17]. Nicholls *et al.*[17] found in their study that 57–67 per cent of patients thought clinically not to have involved nodes were found by the pathologist to be node negative while about two-thirds thought to have involvement by the clinician had this status confirmed by the pathologist. The registrars correctly identified two of 25 cases (8 per cent) with lymphatic metastases while two specialist clinicians correctly identified node positive patients in 12 of 24 (50 per cent) and 15 of 27 (55 per cent) cases respectively.

Other radiological techniques have been used to try to predict nodal involvement. These include iliopelvic lymphoscintigraphy[28,29], monoclonal immunoscintigraphy[30–32], CT[24,33–37] and more recently nuclear magnetic resonance[38,39]. Thus far, simple lymphoscintigraphy has been disappointing and the position of immunolymphoscintigraphy is yet to be fully established[28–32].

CT studies suggest that only nodes of ⩾1 cm can be identified[24,33–37]. Node size is, of course, no indication of involvement with tumour and may just represent reactive changes. Nuclear magnetic resonance has been shown to be as specific but less sensitive than CT in the prediction of nodal involvement[38]. However, it is a new technique and further experience is needed for a more complete evaluation of its role.

Table 3 *The accuracy of endosonography in predicting mesorectal nodal involvement*

	No. of patients	No. correct	Accuracy (%)
Hildebrandt *et al.*[22]	27	20	74
Rifkin and Wechsler[24]	81	70	86
Saitoh *et al.*[21]	71	52	73
Beynon *et al.* (current data)	95	79	83

Three reports on the effectiveness of ES in the detection of mesorectal nodes have appeared in the literature[21,22,24]. Saitoh *et al.*[21] reported an accuracy of 73·2 per cent for the node positive group and 82·3 per cent for the node negative group (19 false positives and three false negatives), although they noted that metastatic and non-metastatic nodes as small as 5 mm could be detected. Hildebrandt *et al.*[22] found that since using a 7 MHz transducer lymph node metastases have been identified. In the 27 patients scanned preoperatively, 12 were thought to have metastatic involvement of pararectal lymph nodes. However, after resection this was confirmed in only six cases while the other six showed reactive changes. One of the histologically involved nodes was not detected endosonigraphically. Rifkin and Weschler[24] identified ten of 15 patients with positive nodes with six false positives in the remaining 66 patients. This gave an overall sensitivity of 67 per cent, specificity of 91 per cent, positive predictive value of 63 per cent and negative predictive value of 92 per cent.

Our results compare well with these reports (*Table 3*). It appears that involved mesorectal nodes can be imaged, although there is a problem with false positive diagnoses. Despite this, in our hands, the level of accuracy is higher than can be offered by CT, and is higher than the reported accuracy of digital examination[17] or nuclear magnetic resonance imaging[38].

The false positive diagnoses of nodal involvement cannot be explained by the architecture of the nodes in the mesorectum but may possibly be explained by a difference in the size of mesorectal nodes. Large reactive nodes often have the endosonographic appearance of involved nodes. In addition blood vessels in cross-section have a similar appearance to nodes and could only be distinguished from them by their tubular or branching appearance when the probe was moved up and down the rectum. Fine needle aspiration, guided by ultrasound, would be one way of determining the true status of a node at ES.

In our experience ES has already influenced management decisions, identifying those patients both suitable and unsuitable for peranal local excision. It may well be that the management of middle- and lower-third tumours of the rectum, which are suitable for restorative low anterior resection, could be influenced by accurate preoperative information about nodal status.

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Value of a risk questionnaire in screening for colorectal neoplasm

The value of a postal questionnaire and of Hemoccult II (Smith Klein Diagnostic Inc., Sunnyvale, California, USA) testing in screening for colorectal neoplasms was compared. In the questionnaire, the subjects were asked about previous treatment for colorectal neoplasm and rectal bleeding during the previous 6 months, specified as to type. All participants were asked to perform Hemoccult II blood testing over 3 days. Of 13 759 randomly selected subjects 9040 (66 per cent) performed the test and returned the questionnaire. Three hundred and fifty-four subjects with a positive Hemoccult II test and/or a proven previous colorectal neoplasm had a full assessment including double-contrast enema and rectosigmoidoscopy to 60 cm. Eighteen carcinomas and 61 adenomas were thus diagnosed. The population was followed for from 20 to 29 months, during which time rescreening was undertaken. An additional 34 subjects with carcinomas and 90 with adenomas were identified during this period. A significant correlation between the presence of a colorectal neoplasm and a previous history of colorectal neoplasm, a positive Hemoccult II and a previous history of bright red bleeding but not dark bleeding was found. The possibility of diagnosing a neoplasm was two, four and 19 times higher in a subject with a previous history of bleeding, a history of colorectal neoplasm,or a positive Hemoccult II respectively. Screening by faecal occult blood testing, therefore, at the moment seems to bethe best and only practicable method.

Keywords: Faecal occult blood, testing, screening, colorectal carcinoma

J. Kewenter, E. Haglind and L. Smith

Department of Surgery, Sahlgrenska Sjukhuset, S-413 45 Goteborg, Sweden

Correspondence to
Dr J. Kewenter

The risk of developing colorectal cancer is increased in some diseases but it is also closely related to age. Thus, the incidence of colorectal cancer in Swedish subjects between 45 and 49 years of age is 15 per 100 000, compared with 131 per 100 000 between 65 and 69 years of age[1] The possibility of curing colorectal cancer with surgery is good if the carcinomas are diagnosed at an early stage. General screening of subjects in higher age groups for this type of cancer has therefore been advocated[2]. The most frequently used method is screening by faecal occult blood testing but risk questionnaires have also been advocated as a useful screening tool[3]. These questionnaires have usually included questions about abdominal symptoms, bleeding, previous colorectal neoplasms and a family history of colorectal neoplasms.

One aim of this study was to determine the value of a questionnaire as a screening tool for early detection of colorectal cancer. The other aim was to determine whether subjects with a history of colorectal neoplasms and/or colorectal bleeding and/or positive Hemoccult II (Smith Klein Diagnostic Incorporated, Sunnyvale, California, USA) constitute special risk groups This investigation was part of a larger screening study for the early detection of colorectal neoplasms with the aid of faecal occult blood testing[4].

Patients and methods

All 27 700 inhabitants of the City of Gothenburg born between 1918 and 1922 (60–64 years of age in 1982) were randomly allocated to a control or a test group. The control group consisted of 13 744 and the test group of 13 759 individuals.

Three Hemoccult II tests, a letter of instruction, a questionnaire and a prepaid reply envelope were mailed out to the subjects in the test group The subjects were asked to perform Hemoccult II occult blood testing with two samples from each of three consecutive stools and mail the slides back to the hospital immediately after the last test occasion Two reminder letters were sent out to subjects who did not answer The last letter included another set of Hemoccult II slides

The test group was divided into two subgroups and slides from older subjects were not hydrated before development while slides from younger subjects were rehydrated The latter persons were asked to maintain a low fruit and vegetable intake for 2 days before sample collection The subjects in both groups were also asked to avoid food made of blood and to avoid vitamin C tablets This was performed in order to study the sensitivity of the test

In the questionnaire, the subjects were asked if they had previously been treated for a colorectal neoplasm and if they had noticed blood from the anus during the 6 months before testing The subjects with bleeding were asked whether the bleeding had been dark or bright red The case notes of those who stated that they had previously been treated for a colorectal neoplasm were collected.

Individuals with one or more positive Hemoccult II tests and/or a previous history of colorectal neoplasm were called to the hospital for assessment This included a digital rectal examination, proctoscopy and rectosigmoidoscopy with a flexible instrument 60 cm long All subjects were then referred for double-contrast enema examination of the colon. Rescreening was offered to all subjects in the test group from 16 to 22 months (mean 20 months) after the first study All slides were rehydrated at the time of rescreening Subjects with negative Hemoccult II test and without a history of neoplasm were not examined.

Follow-up of all subjects was achieved by continuous quarterly contact with the Cancer and Death Registry, weekly contact with the three departments of surgery in the City of Gothenburg and continuous contact with the register at the Department of Pathology. Through these registers it was also possible to follow up the few subjects who moved to other localities in Sweden It should be pointed out that the Swedish health care system covers the vast majority of all hospital care In this system the patient is normally treated in his local hospital and only at other hospitals if referred. By these routines, it was judged virtually impossible for a person in our studied groups with a diagnosed colorectal neoplasm to be lost to follow-up The average follow-up of patients was 24 months (20–29 months), including the rescreening period.

All excised neoplasms were examined by the same pathologist

New batches of Hemoccult II were evaluated at the Reference Laboratory for Fecal Occult Blood Testing, Memorial Sloan Kettering Cancer Centre, New York City, USA.

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Table 1 *The results of the assessment in subjects with positive Hemoccult II*

	Positive history				
	Bright blood only	Dark blood only	Previous neoplasm +blood	Previous neoplasm	Negative history
n	797	345	22	50	7826
Positive Hemoccult	72	13	3	3	258
Assessed	68	13	3	3	217
Neoplasm	28	0	0	2	46
Cancer	6	0	0	0	12
Adenoma	22	0	0	2	34

Table 2 *The results of assessment and follow-up during 24 months of subjects with a positive questionnaire*

	Bright blood	Dark blood	Previous operation but no bleeding
n	818	346	50
Neoplasm	46	3	5
Cancer	11	0	0
Adenoma	35	3	5
Positive predictive value (%)	5·6	0·9	10·0

Statistical methods

The correlation between each of four variables and the presence of neoplasm was tested with Fisher's exact test. The same test was also used for testing the correlations between the four variables. In order to test the correlation between a variable and presence of neoplasm, eliminating the influence of another variable, Mantel's test was used[5]. Finally, the probability of neoplasm was estimated as a function of the variables significantly correlated to presence of neoplasm by applying a logistic model[6]. All tests were two-tailed.

The probability of neoplasm was estimated as a function of A (0 if no previous colorectal neoplasm, 1 otherwise), BC (0 if no blood or dark blood, 1 if bright red blood) or D (0 if Hemoccult II negative, 1 otherwise) by assuming that the probability is $(1+\mathrm{Exp}(-C_1A-C_2BC-C_3D-C_4))^{-1}$, were C_1, C_2, C_3 and C_4 are constants.

For any combination of the values of the variables A, BC and D, the probability of neoplasm can be calculated by means of the model and the estimated constants. There are eight combinations. The constants obtained were used to calculate the level of risk for the different factors.

Results

Of the 13 759 subjects in the test group 9040 returned the slides and the questionnaire (66 per cent) and 1687 more returned the questionnaire only. This study refers only to those who returned both Hemoccult II and the questionnaire. Of these 9040 subjects 1164 (12·9 per cent) had noticed blood from the anus at least once during a 6-month period before the testing. Of these, 22 had been treated for a colorectal neoplasm. Another 50 subjects had previously been treated for colorectal neoplasm but had no history of rectal bleeding (*Table 1*). Eighty-eight subjects who had noticed blood (7·6 per cent) had a positive Hemoccult II test. Three of the subjects with a history of a colorectal neoplasm but without a history of rectal bleeding also had a positive Hemoccult II test. The result of the complete assessment (304) among those with a positive (Hemoccult II) test (349) is shown in *Table 1*. It can be seen from *Table 1* that all subjects with diagnosed neoplasm and a history of bleeding had noticed bright blood. None had noticed dark blood.

The results of the assessment and follow-up during 24 months of subjects with a positive questionnaire are shown in *Table 2*. In 818 subjects with bright bleeding the positive predictive value for neoplasm was six times higher than among the 346 subjects who had noticed dark bleeding.

Of the subjects with a positive Hemoccult II, 91 had a positive history (bleeding and/or previous colorectal neoplasm) while 258 subjects with a positive Hemoccult II had neither noticed any bleeding nor had any history of colorectal neoplasm (*Table 3*). The number of diagnosed neoplasms at the first and second screening and in the interval between the two screening occasions (24 months) is shown in *Table 3*. The number of subjects in the group with a negative Hemoccult II test but with a positive history during the same period is also shown in the table. The positive predictive value was twice as high among the subjects with a positive Hemoccult II test and a positive history compared with those who had a positive Hemoccult II test but a negative history, and 19 times higher than for those with a negative Hemoccult II and a positive history (*Table 3*).

In the questionnaire, 149 subjects stated that they had previously been treated for a colorectal neoplasm. When the hospital records were studied only 72 had in fact been treated for a colorectal neoplasm. Of these, 21 had previously been operated on for colorectal cancer, 22 for tubular adenomas and nine for tubovillous adenomas. The microscopic report could not be found in the remaining 20 subjects with benign adenomas. Thus, a misconception about the diagnosis among the 149 subjects occurred in no less than half of them (72 of 149 subjects). Anal polyps, haemorrhoids and hyperplastic noduli were the main reasons for the misconceptions. Of the 72 subjects with a proven history of previous colorectal neoplasm, 22 had noticed blood from the anus during the last 6 months (*Table 1*).

All 72 subjects with a previous history of colorectal neoplasm were later called separately for a reassessment. Four of these subjects, however, had died by the time of follow-up, nine subjects did not want to participate and another three could not be located. Thus, 56 of the 72 subjects participated in the review. Five adenomas were diagnosed among these 56 subjects at the initial screening and two more during the follow-up. Two of these adenomas were found among the subjects with a positive Hemoccult II test.

The calculations for demonstrating possible correlations between the presence of neoplasms and the different variables are based on the figures in *Table 4* and the results of these calculations are shown in *Tables 5, 6* and *7*.

It will be seen from *Table 5* that there is an increased possibility of finding a neoplasm in a subject who has a history of colorectal neoplasm, a history of bleeding or a positive Hemoccult II. There was a significant correlation with the presence of a neoplasm if the bleeding was bright but not if the bleeding was dark. However, it cannot be excluded that these correlations were due to one or more of the factors which were alone strong enough to be responsible for the different results. Each variable was therefore tested in such a way that the influence of other variables was eliminated. This was done after the correlations between the variables had been tested (*Table 6*). All variables were significantly correlated except a history of colorectal neoplasm and the result of Hemoccult II testing. There was a positive correlation between the presence of a colorectal neoplasm and a history of colorectal neoplasm, a positive

Table 3 *The number of diagnosed neoplasms at the first and second screening and during the interval between the two screening occasions*

	Positive Hemoccult II + negative history	Positive Hemoccult II + positive history	Negative Hemoccult II + positive history
n	258	91	1123
Neoplasm	47	33	21
Cancer	13	8	3
Adenoma	34	25	18
Positive predictive value (%)	18·2	36·3	1·9

Table 4 *Number of subjects with carcinomas or adenomas in groups with and without history of neoplasm or bleeding or a positive Hemoccult II test*

			Number of subjects	Carcinomas	Adenomas
*A*0	*B*0	*D*0	7568	28	74
*A*0	*B*0	*D*1	258	13	34
*A*1	*B*0	*D*1	3	0	2
*A*1	*C*1	*D*1	3	0	0
*A*1	*C*2	*D*1	0	0	0
*A*0	*C*1	*D*1	72	8	23
*A*0	*C*2	*D*1	13	0	0
*A*0	*C*1	*D*0	725	3	10
*A*0	*C*2	*D*0	332	0	3
*A*1	*C*1	*D*0	18	0	2
*A*1	*C*2	*D*0	1	0	0
*A*1	*B*0	*D*0	47	0	3
Total			9040	52	151

A, previous colorectal neoplasm (no = 0, yes = 1); *B*, colorectal bleeding (no = 0, yes = 1), *C*, bright blood (= 1) or dark blood (= 2), *D*, Hemoccult II (negative = 0, positive = 1)

Table 5 *Test of correlation between the different variables* A, B, C, *and* D *and the presence of a colorectal neoplasm*

Test of correlation between presence of neoplasm and variable	Two-tailed *P* value obtained by Fisher's exact test
A	0·002
B	<0·001
*BC*1	<0·001
C	<0·001
*BC*2	0·195
D	<0·001

A, previous colorectal neoplasm (no = 0, yes = 1), *B*, colorectal bleeding (no = 0, yes = 1); *C*, bright blood (= 1) or dark blood (= 2), *D*, Hemoccult II (negative = 0, positive = 1), *BC*1 (0 if *B* = 0, 1 if *C* = 1), bright bleeding, *BC*2 (0 if *B* = 0, 1 if *C* = 2), dark bleeding There is an increased chance of finding a neoplasm in subjects who have a history of colorectal neoplasm, a history of bleeding or a positive Hemoccult II test There was a significant correlation if the bleeding was bright but not if the bleeding was dark

Hemoccult II and bright red bleeding, but not dark bleeding (*Table 7*)

The probability of colorectal neoplasm was estimated as a function of these variables by means of a logistic model (see statistical methods). The estimation of the constants gave the following result. C_1 1·28, C_2 0·72, C_3 2·93, C_4 −4·35. It was found that the possibility of diagnosing a colorectal neoplasm was four times higher in subjects with a history of colorectal neoplasm than in subjects without such a history, twice as high if the subjects had a history of colorectal bleeding and 19 times higher if they had a positive Hemoccult II as opposed to a negative Hemoccult II test.

Details concerning the incidence of neoplasia in the test and control groups, the distribution of the carcinomas according to Dukes' classification, the number of neoplasms found at re-screening, the site and size of the lesions and the sensitivity and specificity in the different groups have recently been published[4,7,8].

Discussion

The most commonly used screening method for colorectal cancer is the guaiac-based test for faecal occult blood. In order to increase the pick-up rate of neoplasms, Hemoccult II testing has in some studies been combined with a risk questionnaire[3] However, questionnaires which are directed towards symptoms seem to be very difficult to construct as symptoms similar to those of colorectal cancer are very common in the community and non-specific in character. Questions concerning clinical symptoms were therefore not included in the present questionnaire.

Macroscopical rectal bleeding is a relatively common symptom in subjects with colorectal neoplasms and a question about it was therefore included. Theoretically, it might be more accurate to investigate those patients with a history of bleeding during a 6-month period before the study instead of investigating those with a positive Hemoccult II test. However, no less than 12·9 per cent of all subjects (1164 of 9040) who answered the questionnaire had noticed blood once or more during a 6-month period before answering the questionnaire. This high percentage makes it practically impossible to investigate everyone with such a history. A similar, high figure was found in one UK study but in another UK study only 6·6 per cent of 527 subjects had noticed bleeding from the back passage during the corresponding time period[9,10]. This difference in incidence of rectal bleeding might be due to a difference in the ages of the two populations. If the group of 1164 subjects with a history of bleeding had alone been assessed only 11 of the 52 colorectal carcinomas and only 25 per cent of the adenomas would have been diagnosed Thus, the vast majority of subjects with colorectal neoplasm in a screened population had not noticed any bleeding. However, as could be expected, the number of neoplasms diagnosed among those with a history of bleeding was significantly higher than in those without such a history and there was a significant correlation between the presence of a neoplasm and colorectal bleeding.

The type of rectal bleeding, dark or bright, has been considered to be predictive of the presence of a colorectal neoplasm[11]. In subjects with neoplasms dark bleeding is considered to be significantly more likely than bright bleeding[11]. However, in our study group, in contrast, a significant correlation was found between the presence of a neoplasm and a history of bright bleeding but not between the presence of a neoplasm and dark bleeding The explanation could be that 'dark

Table 6 *Test of correlation between the different variables*

Test of correlations between variables	Two-tailed *P*-value obtained by Fisher's exact test
A and *B*	<0·001
A and *D*	0·115
A and *C*	0·009
B and *C*	<0·001
C and *D*	0·001

A, previous colorectal neoplasm (no = 0, yes = 1), *B*, colorectal bleeding (no = 0, yes = 1), *C*, bright blood (= 1) or dark blood (= 2), *D*, Hemoccult II (negative = 0, positive = 1) All variables were significantly correlated except a history of previous colorectal neoplasm and the result of Hemoccult II testing

Table 7 *Test of correlation between the different variables and the presence of a neoplasm when the influence of other variables had been eliminated*

Test of correlation between presence of neoplasm and variable	Eliminating the influence of variable	Two-tailed Mantel's test (*P* value)
A	*B* and *C*	0·012
B	*A*	<0·001
C	*A*	<0·001
B	*D*	<0·009
C	*D*	0·004
D	*B* and *C*	<0·001

A, previous colorectal neoplasm (no = 0, yes = 1), *B*, colorectal bleeding (no = 0, yes = 1), *C*, bright blood (= 1) or dark blood (= 2); *D*, Hemoccult II (negative = 0, positive = 1) bleeding' was synonymous with dark faeces in some cases where the 'dark' faeces were not due to blood. It is possible that a higher correlation with bleeding and colorectal neoplasm would have been achieved using a more detailed questionnaire. However, the difficulty in predicting the presence of colorectal neoplasms from the type of rectal bleeding has been clearly shown[11].

Patients who have had a colorectal neoplasm are considered to have an increased risk of developing a new colorectal neoplasm[12]. It therefore seemed logical to include a question about the presence of previous colorectal neoplasms in the questionnaire. One hundred and forty-nine subjects answered that they had previously been treated for a colorectal neoplasm. We checked this information with the department where these subjects had been treated. It was then found that the diagnosis was correct in only half of the subjects (72 out of 149). Thus, half of the subjects were unfortunately unaware of the reason for their previous treatment. We conclude that it is necessary to confirm objectively the case history concerning previous neoplasms before the subject is called for a check-up based upon information obtained in a questionnaire. There is a significantly increased chance of diagnosing a new colorectal neoplasm if the subject has a proven history of colorectal neoplasm. The risk was estimated to be four times higher than in those without such a history.

The use of a questionnaire entails a lot of work. The work involved in checking the information about previous treatment for colorectal neoplasms and the very high number of subjects in these age groups with a history of bleeding makes a questionnaire unsuitable as a screening tool, considering its low specificity and sensitivity. It is possible that reformulation of the questions and other types of questions would have yielded more pertinent information. The chance of diagnosing a colorectal neoplasm was four times higher in a subject with a previous history of colorectal neoplasm than in one with no such history and twice as high in subjects with a history of bleeding than with no history of bleeding, but the chance of diagnosing a neoplasm was 19 times more likely if the Hemoccult II test was positive than if it was negative Screening for early detection of colorectal neoplasms by faecal occult blood testing therefore seems to be the best and only practicable method.

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Adjuvant therapy of poor prognosis colon cancer with levamisole: results of an EORTC double-blind randomized clinical trial

J.-P. Arnaud, M. Buyse*, B. Nordlinger†, F. Martin‡, J.-C. Pector§, P. Zeitoun¶ A. Adloff and N. Duez*

*C.M.C.O., Strasbourg, †Hôpital Saint-Antoine, Paris, ‡INSERM Unité 252, Dijon, and ¶C H U. Robert Debré, Reims, France; *European Organization for Research and Treatment of Cancer Data Center and the §Institut Jules Bordet, Brussels, Belgium*

Correspondence to.
Mr M. Buyse, European Organization for Research and Treatment of Cancer Data Center, 125 boulevard de Waterloo, B 1000 Brussels, Belgium

From 1978 to 1985, 297 patients were entered in a double-blind randomized trial comparing levamisole to placebo as adjuvant therapy of Dukes' C carcinoma of the colon. Therapy consisted of from two to five tablets of 50 mg levamisole (or placebo) twice a week, depending on bodyweight for 1 year. Levamisole was generally well tolerated, with only four reversible cases of agranulocytosis reported among 129 patients. The trial failed to show a benefit of levamisole on disease-free survival ($P = 0{\cdot}53$) *or on survival* ($P = 0{\cdot}35$). *There was no difference between the two treatment groups in terms of number of disease relapses, sites of relapse, or time to relapse. The proportion of patients still alive at 5 years was 51 per cent (standard error, 5·5 per cent) in the levamisole group* versus *39 per cent (standard error, 5·4 per cent) in the placebo group.*

Keywords: Randomized clinical trial, double-blind treatment, colon neoplasm, immunotherapy

Colon carcinoma is second only to lung cancer as a cause of cancer-related deaths in the USA and western Europe[1] Despite intensive investigation, the results of treatment for colon cancer remain poor and have changed little in the last three decades. Surgical treatment is the primary management of colorectal tumour with roughly 80 per cent of the patients being operable at the time of diagnosis[2,3]. Even when resection is considered curative, the overall 5-year survival is only 50 per cent[4,5].

The prognosis of patients with colon cancer is clearly related to the extent of tumour spread at the time of diagnosis, as assessed by the classification of Dukes[6] or its later modifications[7]. The proportion of patients alive 5 years after surgery is of the order of 80 per cent for tumours confined to the submucosa (Dukes' A), 60 per cent for tumours penetrating deeper into the bowel wall (Dukes' B_1), 45 per cent for tumours extending through the serosa into the pericolic fat (Dukes' B_2), and as little as 25 per cent if there is regional lymph node involvement (Dukes' C)[8–10]. Thus patients with regional lymph node involvement must be considered as potentially having occult disseminated disease even when their primary tumour has been resected for cure and are therefore ideal candidates for adjuvant therapy.

At the time this trial was started (1978), the benefit of adjuvant chemotherapy in colorectal cancer was unclear, and the question has remained controversial[2,11–14]. Promising results had been published on the use of immunotherapy both in the advanced disease and in the adjuvant setting. The main agents investigated were Bacillus Calmette-Guérin (BCG), methanol extracted residue of BCG (MER), *Corynebacterium parvum* and levamisole. BCG had been used in advanced intestinal cancer[15] and as adjuvant to surgery in colon cancer patients with lymphatic extension[16,17]. MER had been used in advanced colorectal cancer patients[18]. *C parvum* had been used in association with chemotherapy in bronchial and advanced breast carcinomas[19]. However, none of these trials was controlled and the interpretation of their results was disputed.

Levamisole is a pure chemical which was first used as an anthelmintic drug. Its effect on the immune response was found by Renoux and Renoux[20] who reported that levamisole enhanced immunization of mice against *Brucella abortus*. Since this first observation, levamisole has been considered to be a modifier of the immune response. Various reports[21] have suggested that levamisole could have an enhancing effect on the functions of B lymphocytes, T lymphocytes or macrophages Levamisole has also been considered to be an antianergic agent, restoring normal immune response in immunosuppressed situations. A restoration of delayed hypersensitivity reactions in cancer patients following levamisole therapy was reported by several investigators[22,23]. Two controlled studies using levamisole had been published before the beginning of our trial, one in patients with resectable bronchial carcinomas[24,25] and one in patients with advanced breast carcinomas[26]. Both of these trials used a fixed dose of 150 mg per day on 3 consecutive days every other week. In the first of these trials, a significant reduction was observed in the number of relapses in patients weighing <70 kg. In the second trial, levamisole was combined with radiotherapy, and led to an apparent reduction in the number of relapses and deaths compared with those of a control group Non-randomized trials of levamisole in the treatment of colorectal cancer[27] and of gastric cancer[28] following tumour resection had suggested a possible improvement in survival, but information from properly randomized trials was lacking.

This prompted the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group to initiate a double-blind randomized clinical trial comparing levamisole to placebo in patients after 'curative' resection of Dukes' C colon cancer.

Patients and methods

Eligibility criteria

Patients were eligible for this trial if they fulfilled all of the following criteria histological confirmation of the presence of primary adenocarcinoma of the colon sited between the caecum and the sacral promontory, curative surgical intervention, without any macroscopic or histological residual tumour tissue, local or metastatic, observed during or after the operation, histologically confirmed involvement of one or more lymph nodes, i.e. Dukes' C classification of the excised tumour The patients were required to have completely recovered from the acute effects of surgery, to have no evidence of infection and to have adequate haematological indexes (white cell count >2000 per mm^3, platelet count $>150\,000$ per mm^3) and adequate renal function (creatinine clearance $>60\ ml\ min^{-1}$) There was no age limit. Patients were excluded in the following cases presence of another cancer, other than basal cell carcinoma of the skin; major mental disturbance, previous history of agranulocytosis or known allergy to drugs, history of ulcerative or granulomatous colitis, or familial polyposis, previous radiotherapy, chemotherapy, or immunotherapy

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Table 1 *Patient characteristics*

	Placebo	Levamisole	Total (%)
Age (years)			
Mean	64	64	64
Range	23–87	29–84	23–87
Sex			
Male	63	70	133 (46)
Female	83	73	156 (54)
Performance status*			
Normal activities (1)	55	55	110 (38)
Restricted activities (2)	74	73	147 (51)
Unable to work (3+)	17	15	32 (11)
Tumour location			
Ascending	31	27	58 (22)
Transverse	22	20	42 (16)
Descending	16	18	34 (13)
Sigmoid	64	69	133 (50)
Tumour extension			
Muscularis	6	10	16 (6)
Subserosa	87	85	172 (60)
Through serosa	37	36	73 (26)
Organs	13	10	23 (8)
Number of positive nodes			
1	42	49	91 (32)
2	26	33	59 (21)
3	15	19	34 (12)
4	19	14	33 (12)
5+	41	23	64 (23)

Values are numbers of patients (except for age). * Reference 48. Percentages are computed on the basis of the number of patients for whom information is available.

Surgery

The surgical excision had to include a removal of the lymphatic drainage by a complete resection of the mesentery of the cancer-bearing segment. The surgeon had to confirm the absence of any cancerous tissue in the peritoneum, the liver and other organs of the abdominal cavity.

Randomization method

Eligible patients were entered on trial immediately after the histological confirmation of a Dukes' C lesion, as soon as possible after surgery. Numbered boxes containing tablets of either placebo or levamisole had been provided to all investigators and were used in sequential order. The EORTC Data Center was informed of a patient's entry into the trial by a telephone call. Placebo or levamisole had been assigned to the successive box numbers at random, using a permuted block design. The boxes and tablets of levamisole were indistinguishable from their placebo counterparts, so that neither the attending physician nor the patient was aware of the actual treatment received.

Placebo or levamisole administration

Tablets containing 50 mg levamisole (or placebo) were taken on the same two consecutive days of each week for a period of 1 year or until evidence of relapse or severe toxic symptoms. The daily dosage of levamisole (or placebo) was adapted to body weight throughout the therapy period: 100 mg daily (i.e. two tablets) for patients weighing <50 kg, 150 mg for those weighing 51–70 kg, 200 mg for those weighing 71–90 kg, and 250 mg for those >90 kg.

Follow-up examinations and criterion of relapse

Standard clinical examinations (including the pelvis and the liver), chest X-rays, and complete blood counts were required before entry into the trial, every month during the first 3 months of adjuvant therapy, and every 3 months during the remaining period. Liver scan, intradermal tuberculin reaction or other immunological tests, rectoscopy, double-contrast barium enema and carcinoembryonic antigen (CEA) measurement were optional at the discretion of the attending physician.

Relapse was defined as any morphological proof of the appearance of tumour by palpation, X-ray, scintigraphy, laparoscopy, colonoscopy or laparotomy. An elevation of CEA level prompted the search for tumour recurrence but was not considered alone as evidence of relapse.

Statistical methods

Survival was measured from the date of surgery for the primary tumour to the date of death from any cause. Disease-free survival was measured from the date of surgery to either relapse or death, whichever occurred first. Survival and disease-free survival curves were estimated by the product-limit procedure of Kaplan and Meier[29], and compared using the log rank test[30]. Comparisons were retrospectively adjusted for prognostic factors using a stratified log rank test. All statistical tests were two-tailed.

Results

Patient cohort

Two hundred and ninety-seven patients were entered into the trial by 19 institutions between April 1978 and December 1985. Institutional problems were encountered in two institutions after entry of five and three patients respectively; these institutions were excluded from the trial and no data could be obtained on their eight patients (placebo, five, levamisole, three). The number of patients available for analysis was thus 289. Seven patients were found to be ineligible after entry to the trial because they had metastatic disease; one patient was found to be ineligible because he had no regional lymph node involvement. These eight ineligible patients (placebo, two; levamisole, six) were included in all analyses to avoid any statistical biases[31]; excluding them from the analyses did not materially affect the results. Adjuvant therapy was never started in eight patients (placebo, two; levamisole, six). These patients were included in all but the toxicity analyses.

At the time of this analysis, the mean follow-up time for surviving patients was 3 years.

Patient characteristics

Table 1 shows the main prognostic features of the patients. The only noteworthy difference between the two treatment groups was the significantly larger number of patients with four or more positive lymph nodes in the placebo group. Detailed data on the tumour histopathology were collected and their prognostic importance will be assessed in a separate paper.

Treatment compliance and toxicity

Adjuvant treatment was started within 2 weeks of surgery for 157 patients (54 per cent), and within 1 month of surgery for 271 patients (94 per cent). There was a sigificant association between the occurrence of a postoperative complication and a delay of more than 2 weeks between surgery and the beginning of adjuvant therapy ($P=0.008$). However, postoperative complications were reported in only 55 patients (19 per cent) and thus could not explain the majority of delays in excess of 2 weeks. Treatment was continued after the 1-year protocol period in 89 patients (31 per cent), for periods up to three additional months (and for as long as 6 and 10 months in two patients).

Table 2 shows the reasons for stopping treatment in both groups. Sixty-one per cent of the patients completed therapy (1 year or more). Four patients refused therapy (all on levamisole) while toxicity prevented further administration in 14 (placebo, two; levamisole, 12). In the 12 patients who stopped taking levamisole, four had agranulocytosis (one with a white cell count as small as 1200 per mm^3 and with 10 per cent neutrophils), two had skin rashes, two had flu-like syndromes,

Table 2 *Reasons for stopping therapy*

	Placebo	Levamisole	Total (%)
End of 1 year treatment	90	87	177 (61)
Disease relapse	33	26	59 (21)
Death without relapse	6	2	8 (3)
Patient refused treatment	0	4	4 (1)
Treatment stopped due to toxicity	2	12	14 (5)
Major protocol violation	2	4	6 (2)
Patient lost to follow-up	6	6	12 (4)
Other reasons	7	2	9 (3)
Number of patients	146	143	289

two had depressive syndromes and two had nausea and vomiting. All patients returned to normal after stopping therapy. The two patients who stopped taking placebo did so because of nausea and vomiting.

The most frequently reported minor side-effects of treatment did not differ between the two treatment groups (*Table 3*).

Disease-free survival

Figure 1 shows the disease-free survival curves up to 7 years. There was no significant difference between the two treatment groups ($P=0{\cdot}53$). There was also no significant difference between the two treatment groups if the comparison was limited to patients in whom adjuvant therapy was initiated within 2 weeks of surgery ($P=0{\cdot}87$). Relapses were histologically confirmed in 67 (placebo, 35; levamisole, 32) of 157 cases (43 per cent). The sites of relapse are detailed in *Table 4*. Relapse occurred at the anastomotic site in 46 of 157 cases (29 per cent). The liver was the first site of relapse in 97 of 157 cases (62 per cent).

Survival

Figure 2 shows the survival curves up to 7 years. The percentage of patients still alive at 5 years was 39 per cent (standard error, 5·4 per cent) in the placebo group *versus* 51 per cent (standard error, 5·5 per cent) in the levamisole group. The difference between the survival curves was not statistically significant ($P=0{\cdot}35$). There was no difference between the two treatment groups if the comparison was limited to patients in whom adjuvant therapy was initiated within 2 weeks of surgery ($P=0{\cdot}86$). Exclusion of the ineligible patients and those who never started taking their treatment (placebo or levamisole), did not affect the survival comparisons ($P=0{\cdot}33$) Subset analyses and retrospective adjustments of the treatment comparisons were performed with the prognostic features of *Table 1*. No subset analysis or adjusted comparison resulted in significant separation of the treatment groups.

Table 3 *Number of patients affected by the most frequently reported side-effects of therapy*

	Placebo	Levamisole	Total (%)
Tiredness	27	29	56 (21)
Insomnia	19	18	37 (14)
Anorexia	20	15	35 (13)
Depression	15	19	34 (13)
Nausea and vomiting	10	20	30 (11)
Patients evaluable for toxicity	140	129	269

Discussion

Treatment compliance and toxicity

Treatment compliance was reported to be excellent (*Table 2*), but no measures were taken to verify that the patients had in fact taken their tablets Levamisole was generally well tolerated, as

Table 4 *Sites of relapse*

	Placebo	Levamisole	Total (%)
Site of relapse			
Anastomosis	30	16	46 (29)
Liver	46	51	97 (62)
Peritoneum	15	17	32 (20)
Lymph nodes	11	13	24 (15)
Lung	6	7	13 (8)
Pleura	2	2	4 (3)
Bone	6	2	8 (5)
Skin	7	0	7 (4)
Central nervous system	4	1	5 (3)
Number of relapses	82	75	157

Percentages are relative to the number of relapses, they do not add up to 100 per cent because of multiple relapse sites

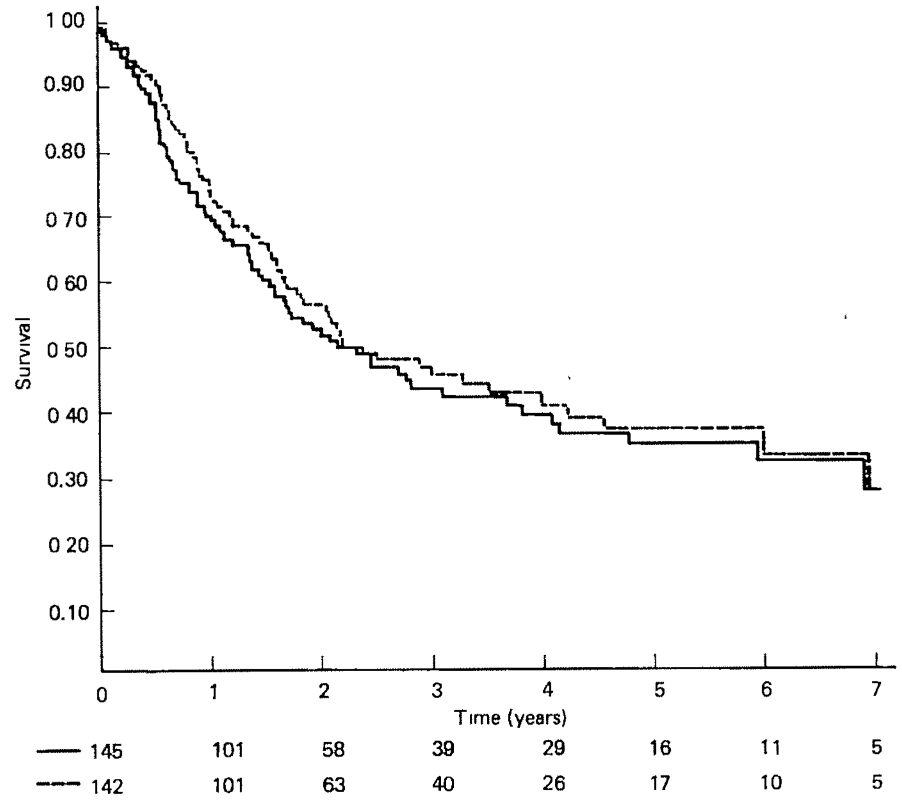
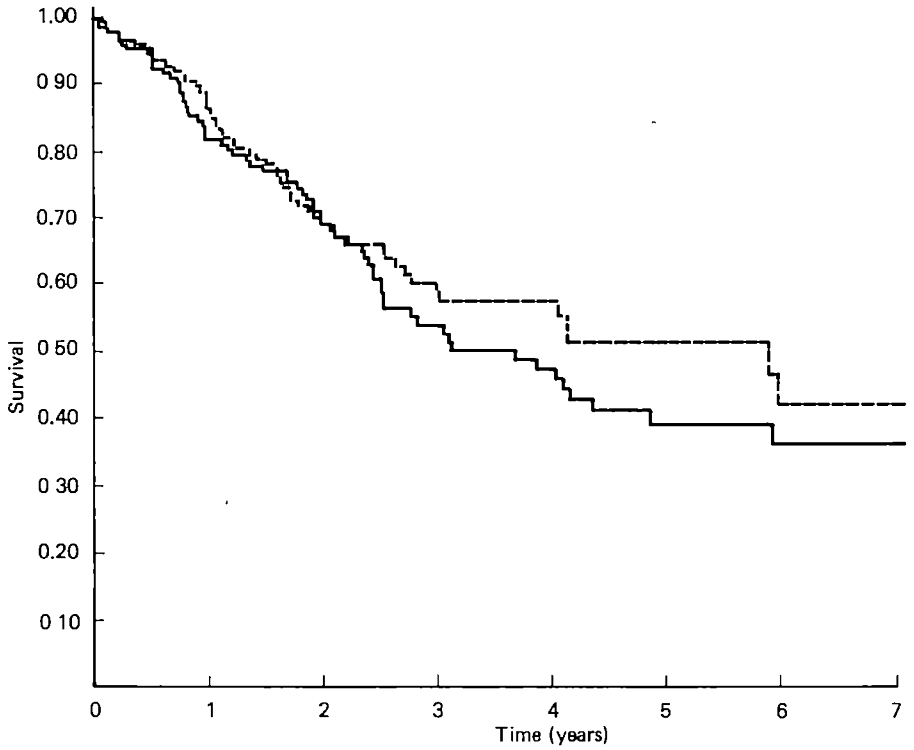


Figure 1 *Disease-free survival curve by treatment group.* ——, *Placebo total number of patients, 145, number of relapses, 82,* –––, *levamisole total number of patients 142, number of relapses, 75,* P=0 53 (*log rank test*)



	0	1	2	3	4	5	6	7
——	145	118	76	45	32	16	11	5
– – –	142	118	72	47	30	18	10	5

Figure 2 *Survival curve by treatment groups ——, Placebo total number of patients, 145, number of deaths, 66, – – –, levamisole total number of patients, 142, number of deaths, 55,* P = 0.35 *(log rank test)*

evidenced by the fact that minor side-effects were reported as frequently in the levamisole as in the placebo group (*Table 3*). Side-effects were considered minor by some authors[32–34], while for others they were an important drawback responsible for interruption of the treatment in over 21 per cent of the cases[35]. In our series, levamisole was stopped for toxicity in only 12 patients of 139 (9 per cent); two of these patients complained of nausea and vomiting, but placebo was also stopped in two other patients with similar complaints. Four of the patients in whom levamisole was stopped had reversible agranulocytosis. This was in line with previous experience with levamisole[33,36,37] None of the patients experiencing agranulocytosis was found to have an autoimmune disease, such as a rheumatoid disorder[38].

Therapeutic results

This trial failed to show a benefit of levamisole over placebo in terms of either disease-free survival or overall survival. This negative result does not exclude the possibility of a small beneficial effect of levamisole. More patients relapsed or died in the placebo group than in the levamisole group, and the observed 5-year survival is 12 per cent better in the levamisole group (51 *versus* 39 per cent). Under reasonable assumptions, this trial had an 80 per cent chance of detecting a difference in 5-year survival of about 18 per cent, and had less than an 80 per cent chance of detecting smaller differences which might none the less be of clinical relevance. However, the fact that the disease-free survival curves were identical in the levamisole and placebo groups (*Figure 1*) makes it unlikely that the difference observed in the survival curves (*Figure 2*) was attributable to any treatment effect, it is more likely to be due to chance fluctuations. In addition, patients with a less favourable prognosis (four or more positive lymph nodes) were by chance randomized to receive placebo, so that if anything the unadjusted treatment comparison may be somewhat biased in favour of the levamisole group.

Our negative result must be interpreted in the context of other clinical trials using similar therapeutic approaches. Few randomized control trials were published on adjuvant immunotherapy for colorectal cancer[14]. One trial compared fluorouracil and radiotherapy with the same regimen plus MER, in Dukes' B and C colorectal cancer; only 73 patients were randomized but the authors claim benefit of immunotherapy in the 44 patients with Dukes' C colon cancer[39,40]. Another trial comparing a control group with groups receiving either fluorouracil or fluorouracil + levamisole was so small, with 52 patients followed for at least 6 months, that its results cannot possibly show any effect[33]. Yet another trial of *C. parvum versus* control was too small to allow any meaningful conclusion (92 patients of whom 26 were Dukes' C)[41]. A large trial comparing four treatment groups consisting of chemotherapy with fluorouracil and semustine, or BCG alone, or both, or no adjuvant therapy was published by the Gastrointestinal Tumor Study Group in stages B_2 and C colon cancer[42]. No significant treatment differences were found among the 572 patients (of whom 340 were Dukes' C) in either recurrence or survival rates. A recently reported trial compared a control group with groups receiving either fluorouracil or fluorouracil + levamisole in Dukes' A, B or C colorectal cancer[43]. A significant survival advantage of fluorouracil + levamisole over both the control group and the group receiving fluorouracil alone was found in the 141 patients analysed, of whom 41 were Dukes' C.

Three further large clinical trials were reported recently, but in abstract form only. The North Central Cancer Treatment Group (NCCTG) compared a control group with groups receiving either levamisole alone or fluorouracil + levamisole in Dukes' B_2 or C colorectal cancer[34] Both arms containing levamisole were found to be superior to the control group in terms of time to progression and survival in the 39 patients analysed. The advantage of therapy was reported to be most striking in Dukes' C patients. The National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP) compared a control group with a group receiving polychemotherapy with fluorouracil, semustine and vincristine, and one receiving BCG alone in Dukes' B and C colon cancer[44]. In this large trial of

1166 patients, BCG administration resulted in no advantage in terms of disease-free survival but in a small yet significant prolongation of survival. The Southwest Oncology Group compared a control group with a group receiving chemotherapy with fluorouracil and semustine, and one receiving the same chemotherapy + BCG in Dukes' B_2 and C colon cancer[45]. There was no overall difference in either survival or relapse-free survival among the 626 patients randomized, though significant benefits of both chemotherapy and chemotherapy + BCG were claimed among the Dukes' B_2 and C_1 patients, but not among the stage C_2 patients.

On the basis of all these results it is not yet clear whether non-specific immunotherapy alone provides any significant benefit in poor prognosis colon cancer Significant benefits were reported mostly in patients receiving a combination of immunotherapy and chemotherapy. The respective impact of each is unclear and any synergism in the two approaches is a hypothesis that deserves further study. Benefits also tended to be reported in series of colorectal cancer patients, with no distinction made between colonic *versus* rectal locations. It is quite possible, though still speculative, that rectal lesions might respond better to therapy than colonic lesions[14] Our results confirm the experience of the Gastrointestinal Tumor Study Group and of the NSABP with a single immunotherapy (BCG) in colon cancer: the overall effect of therapy, if any, is probably small so that other adjuvant approaches must be considered[42,44]. Whether our results are at variance with those of the NCCTG is still an open question[34] A meta-analysis of all related clinical trials of immunotherapy in colorectal cancer will be most useful when the more recent trials are mature[14].

Our own series presented several advantages: first, it was relatively homogeneous, as only Dukes' C colon tumours were considered for inclusion in the trial. To control further for the remaining heterogeneity among the patients entered, careful examination of the resected tumours was performed and detailed data on histopathology were available for analysis of their prognostic influence. No analysis of treatment results in subgroups appeared to yield outstanding results, however. These analyses were not presented in this paper because we believe that in most instances they confuse rather than clarify the issue, given the great likelihood of spuriously large treatment effects occurring by chance in some of the subgroups examined[46].

Secondly, treatment was given in a double-blind manner, and therefore the possibility of bias in evaluating treatment results in terms of disease relapse was minimal. Because the assessment of relapses is often somewhat subjective (unless it is histologically confirmed, as was the case in less than half of the patients in our series), the possibility of bias must be borne in mind when evaluating the results of non-blinded trials.

Thirdly, the dose of levamisole was related to the weight of the patient in order to reach the optimal daily dose suggested by Amery[25], i.e. about 2·5 mg kg^{-1} day^{-1}. Treatment was initiated as soon as possible after surgery, taking into account the delays due to the histological classification of the resected specimen and/or any postoperative complications. Treatment was started within 2 weeks of surgery for more than half of the patients. Timing could have been important, because levamisole administration can partially reverse the depression of the cell-mediated immunity observed immediately after surgery[47]. However, no significant effect of levamisole was seen on survival or disease-free survival in the patients who started receiving the adjuvant therapy within 2 weeks of surgery Thus the lack of a significant benefit of levamisole in the present study was probably independent of the early or delayed administration of the drug. Furthermore, it can be argued that depression of the immune response is not confined to the immediate postoperative period in cancer patients so that levamisole could potentially have acted on the immune response throughout the entire period of administration.

Finally, treatment consisted only of immunotherapy, with no concurrent chemotherapy. Thus no interaction between the immune modulation and other cellular mechanisms (e.g. cytotoxicity) could have obscured or enhanced any possible benefit of the administration of levamisole.

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A common pathophysiology for full thickness rectal prolapse, anterior mucosal prolapse and solitary rectal ulcer

Anorectal pressures at rest, during conscious contraction of the external sphincter, during serial distension of the rectum and during straining to inflate a balloon were measured in 56 patients (21 patients with full thickness rectal prolapse, 24 patients with anterior mucosal prolapse, 11 patients with solitary rectal ulcer) and in 30 normal subjects. Both basal and squeeze pressures were significantly lower in the three groups of patients compared with matched normal controls ($P<0{\cdot}05$)*. During increases in intra-abdominal pressure, anal pressure remained above maximum rectal pressure* ($P<0{\cdot}05$) *in normal controls, with the highest anal pressures being recorded in the most caudal anal channels. In contrast, anal pressures tended to be lower than rectal pressures during this manoeuvre in patients with rectal prolapse, anterior mucosal prolapse and solitary rectal ulcer, and the highest pressures were recorded in the channels nearest the rectum. During serial distension of the rectum, 64 per cent of patients with solitary rectal ulcer, 75 per cent with anterior mucosal prolapse and 76 per cent with rectal prolapse, but only 10 per cent of controls, showed repetitive rectal contractions. The highest anal pressure always remained higher than rectal pressure during rectal distension in normal subjects* ($P<0{\cdot}05$) *but not in patients. The threshold rectal volume required to cause a desire to defaecate and the maximum tolerable volume were significantly lower* ($P<0{\cdot}05$) *in each of the patient groups, compared with normal subjects. The similarity in the results from patients with rectal prolapse, anterior mucosal prolapse and solitary rectal ulcer support the hypothesis that they share a common pathophysiology. In each of the groups, the rectum is hypersensitive and hyper-reactive, and weakness of the anal sphincter creates the conditions for prolapse of the rectum to occur into or through the anal canal.*

Keywords: Solitary rectal ulcer, anterior mucosal prolapse, full thickness rectal prolapse, rectum, anal sphincter, electromyography

Wei Ming Sun, N. W. Read, T. Carmel Donnelly, J. J. Bannister and A. J. Shorthouse

Subdepartment of Human Gastrointestinal Physiology and Nutrition, University of Sheffield, Floor K, Royal Hallamshire Hospital, Sheffield S10 2JF, UK

Correspondence to.
Professor N. W Read

Anterior mucosal prolapse and solitary rectal ulcer are often found in association[1–5] Their pathogenesis is not understood, though it is often assumed that redundant anterior rectal mucosa enters and plugs the anal canal preventing normal defaecation and inducing anal discomfort and a feeling of incomplete evacuation[4]. Solitary rectal ulcer is thought to occur when the redundant mucosa becomes traumatized and ischaemic within the anal canal[1]. Surgical treatment of anterior mucosal prolapse is often aimed at fixation of the mucosa to the rectal wall by injections of sclerosant or by resection of the redundant rectal mucosa[4], although rectopexy may be preferable for solitary rectal ulcer Although such treatments may be effective in the short term, their long-term benefits are poor[6,7]. It has been suggested that anterior mucosal prolapse may progress to full thickness rectal prolapse[8]. The latter is also associated with 27–49 per cent of cases of solitary ulcer[8–10]. These three conditions may therefore share a common pathophysiology. In support of this suggestion, patients with full thickness rectal prolapse, anterior mucosal prolapse, or solitary rectal ulcer often complain of incontinence[6,11], usually have abnormal descent of the pelvic floor on straining[12,13] and show electrical evidence of reinnervation of the external anal sphincter[11,12,14].

The aims of these series of experiments were to provide further insights into the pathophysiology of the three conditions and to test the hypothesis that each might represent different stages in the same pathophysiological process. Manometric and electrophysiological measurements were carried out under resting conditions, during a voluntary squeeze, during distension of the rectum with a balloon and during increases in intra-abdominal pressure produced by asking the subjects to inflate a balloon.

Patients and methods

Patients

Studies were carried out on a total of 54 women, aged between 22 and 86 years (median 60 years) Nine patients (aged 22–73 years, median 53 years) had a solitary rectal ulcer which was defined as a discrete area of ulceration on the anterior rectal mucosa which showed the typical histological features[5,10,15] Twenty-four patients (aged 34–78 years, median 55 years) had anterior mucosal prolapse, which was identified at proctoscopy as redundant anterior rectal mucosa which appeared at the anal margin if the patient strained Twenty-one patients (aged 38–86 years, median 72 years) had an overt full thickness rectal prolapse extending beyond the anal verge All patients tested showed evidence of abnormal perineal descent in that the pelvic floor descended to more than 2 cm below the pubococcygeal line when the patient strained[14]. Seventy-two per cent (67 per cent solitary rectal ulcer, 71 per cent anterior mucosal prolapse, 76 per cent rectal prolapse) of these patients had had vaginal deliveries, and 35 per cent (33 per cent solitary rectal ulcer, 38 per cent anterior mucosal prolapse, 33 per cent rectal prolapse) had

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had more than three children. Twenty-eight per cent of the patients (33 per cent solitary rectal ulcer, 29 per cent anterior mucosal prolapse, 24 per cent rectal prolapse) were nulliparous. Two men with solitary rectal ulcer (aged 29 and 33 years) were also studied Six patients with anterior mucosal prolapse (25 per cent), four patients with solitary rectal ulcer (36 per cent) and 14 patients (67 per cent) with rectal prolapse also complained of faecal incontinence

For comparison, tests were also carried out on 20 normal female subjects (aged 26–54 years, median 43 years) and ten normal male subjects (aged 19–40 years, median 23 years) None of these subjects suffered from faecal incontinence or had any disease of the anal sphincter or the colon.

All subjects and patients gave their written informed consent for the study The protocol was approved by the Ethical Subcommittee of the Sheffield Health Authority

Methods

A complete history was taken from each patient Careful digital, sigmoidoscopic and proctoscopic examinations of the anorectum were conducted The degree of perineal descent was assessed by proctography[14] or by perineometry[16]. All patients and controls underwent dynamic tests of anorectal function using simultaneous multiport manometry and external sphincter electromyography (EMG) No bowel preparation was used before the test, although patients were invited to empty the rectum if they felt the need to do so.

With the subject lying in the left lateral position and the hips flexed to 90°, a seven lumen polyvinyl catheter, which had an external diameter of 4 mm and which terminated in a small latex balloon, was inserted into the anal canal so that manometric side-holes were situated in the anal canal at 0·5, 1, 1·5, 2 and 2 5 cm and in the rectum at 4·5 cm from the anal verge, the balloon was situated 8 cm from the anal margin. The side-holes were perfused with water at a rate of 0 4 ml/min using a low compliance pressurized perfusion system (Mui, PIP2, Mississauga, Toronto, Canada). Pressures were recorded by pressure transducers (Statham, 230B, Oxnard, California, USA), which were situated in each infusion line and connected via amplifiers to a chart recorder (Hewlett-Packard Co., Waltham, Massachusetts, USA)

The electrical activity of the external anal sphincter was measured using a bipolar wire electrode which was inserted without anaesthetic through the skin into the superficial aspect of that muscle[17,18] The EMG signal was integrated, and both raw and integrated records were displayed on the chart recorder.

Protocol

Resting sphincter pressures and electrical activity were measured for 15 min, during which time the pressures gradually fell in the outermost anal channels The pressures in the anal canal at the beginning and the end of the 15-min period were recorded as the maximum and minimum basal pressures respectively The subject was then instructed to contract the external sphincter as strongly as possible and to maintain the contraction for at least 20 s This was repeated on two further occasions with a rest period of 1 min between each contraction After a gap of at least 5 min, the rectal balloon was inflated with increasing volumes of air (10, 20, 40, 60 and 100 ml). Each inflation was maintained for 1 min, whereupon the balloon was deflated and a gap of at least 1 min was allowed before the next inflation The presence or absence of transient sphincter relaxation, an increase in activity of the external anal sphincter or an increase in rectal pressure were noted. An index of external anal sphincter activity during rectal distension was calculated by multiplying the voltage of electrical activity by the duration of its activity. During each distension, subjects were asked to report if they perceived the distension and to grade the sensation as a feeling of wind, a feeling of stool in the rectum, a desire to defaecate, an urgent desire to defaecate, or pain

The subject was allowed to rest for at least 5 min and was then instructed to increase the intra-abdominal pressure by blowing up a balloon This was carried out on three occasions separated by a rest period of 1 min, and the anorectal pressures and electrical activity of the external anal sphincter were recorded. Any leakage of fluid or faeces that took place during this manoeuvre was noted

Statistical analysis

An analysis of variance was used to test for differences in sphincter pressure and responses to rectal distension and increases in intra-abdominal pressure among the groups If the analysis of variance showed statistical significance, the Student's *t* test was used to determine the levels of significance. The χ^2 test was used to compare the percentage of subjects in each group that showed anal relaxation and repetitive rectal contractions during rectal distension

Results

Basal and sphincter squeeze pressures

After insertion of the catheter, the basal pressure fell slowly to a stable low level over 15 min. The maximum basal pressures recorded shortly after insertion of the catheter ($P < 0{\cdot}01$) and the maximum squeeze pressures ($P < 0{\cdot}01$) at all anal ports were significantly lower in patients with rectal prolapse, anterior mucosal prolapse and solitary rectal ulcer than in normal subjects (*Figure 1*). The minimum basal pressures were also significantly lower in all patient groups compared with normal subjects (*Figure 1*), but only at 1 and 0·5 cm from the anal margin ($P < 0{\cdot}05$). Patients with full thickness rectal prolapse had significantly lower maximum basal pressures than patients with solitary rectal ulcer and anterior mucosal prolapse, though there were no significant differences in maximum squeeze pressures or minimum basal pressures between these groups. Men with solitary rectal ulcer also showed abnormally low maximum basal pressures (34 cmH_2O and 52 cmH_2O, normal range 51–113 cmH_2O) and maximum squeeze pressures (126 cmH_2O and 170 cmH_2O, normal range 178–308 cmH_2O) compared with men in the control group.

Anorectal pressure responses to rectal distension

Distension of the rectal balloon in normal subjects usually caused reductions in pressure at all anal ports (*Figure 2a*), increasing in amplitude and duration as the distending volume increased. These anal relaxations were associated with increases in rectal pressure and transient increases in the electrical activity of the external anal sphincter that became more prolonged as the distending volume and duration of relaxation increased The anal pressure recorded during balloon distension was termed the residual pressure and lowest values always occurred at distension volumes ≥ 60 ml. On deflating the balloon, the anal pressure often showed a rebound increase to values that exceeded the preinflation pressure. Although the rebound was occasionally associated with a brief increase in the electrical activity of the external anal sphincter, it always exceeded the latter in duration, suggesting that it was caused predominantly by increased activity in the internal sphincter. The amplitude of the rebound pressure increased as distending volume increased, and thus resulted in increases in the anal pressures occurring before the next inflation (preinflation pressures)

Rectal distension with increasing volumes of air decreased anal sphincter pressure in all normal subjects and in all patients with solitary rectal ulcer, but in only 10 per cent of patients with rectal prolapse and 30 per cent patients with anterior mucosal prolapse ($P < 0{\cdot}02$, compared with either controls or solitary rectal ulcer) The absent anal relaxation during rectal distension was associated with very low preinflation pressures and hence the observation suggested impaired internal sphincter function. When anal relaxation was seen in patients with the three conditions, this took place at higher volumes of distension, when the rebound phenomenon increased the pressure immediately before the next inflation

Most of the patients with rectal prolapse and anterior mucosal prolapse showed increases in anal pressures during rectal distension (*Figure 2b*) These increases in pressure were associated with bursts of activity in the external anal sphincter. External anal sphincter indices were significantly higher ($P < 0{\cdot}05$) in patients with solitary rectal ulcer and anterior mucosal prolapse than in controls during rectal distension with volumes of 10–100 ml and in patients with rectal prolapse during rectal distension with volumes of 10 and 20 ml (*Figure 3*), but despite this the residual anal pressures were no higher in any of the patient groups compared with the controls (*Table 1*)

The highest preinflation and rebound anal pressures were significantly higher in normal subjects than in each of the patient groups ($P < 0{\cdot}05$, *Table 1*) Normal subjects showed a gradient in residual pressures increasing towards the outermost channels. This gradient was not present in women with solitary rectal ulcer and rectal prolapse and men with solitary rectal ulcer. The

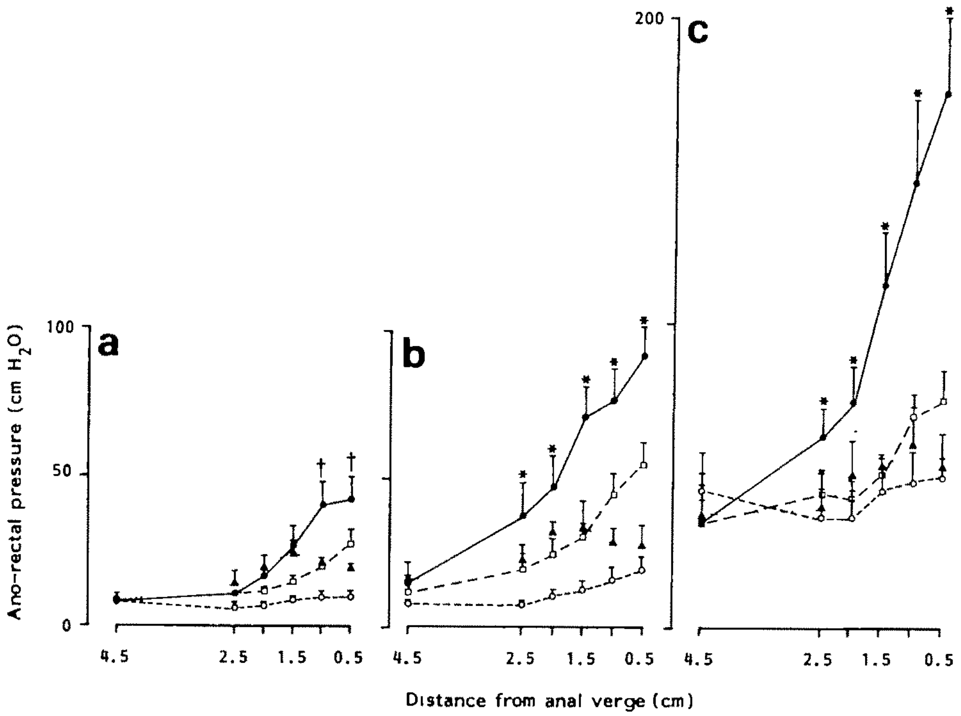

Figure 1 a *Minimum basal pressure*, b *maximum basal pressure and* c *squeeze pressure recorded 0·5, 1·0, 1·5, 2·0, 2·5 and 4·5 cm from anal margin in normal subjects* (●) *and patients with solitary rectal ulcer* (▲), *anterior mucosal prolapse* (□) *and rectal prolapse* (○). *Results are shown as mean* $\pm$*s.e.m.* * *Values in each of the patient groups are significantly lower than in normal subjects.* $P<0{\cdot}01$, † $P<0{\cdot}05$

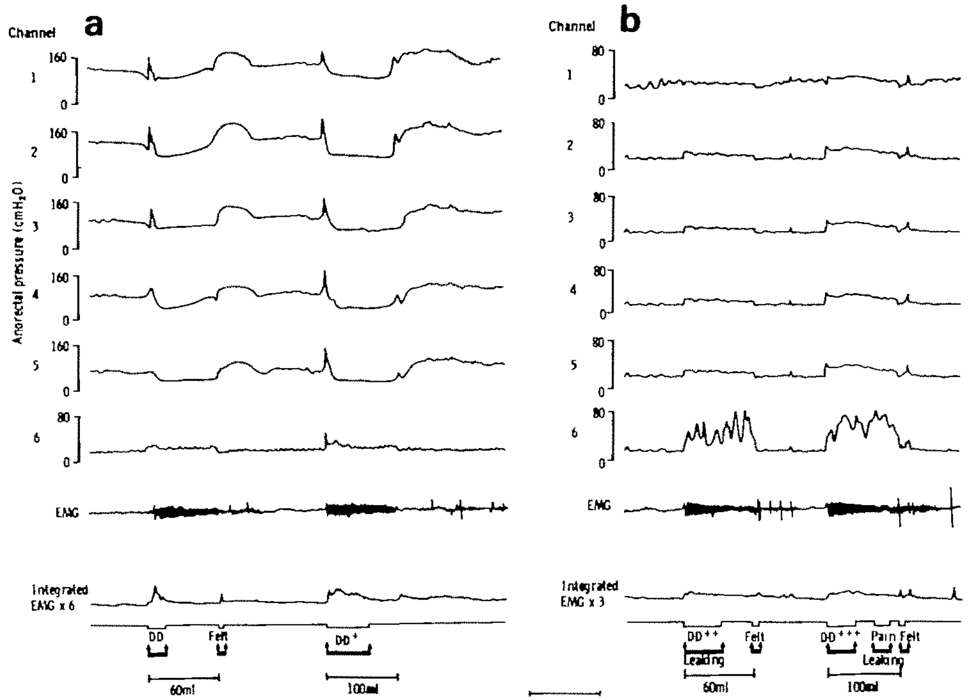

Figure 2 *Recordings of anorectal pressure and of the electrical activity of the external anal sphincter before, during and after inflation of a rectal balloon with 60 and 100 ml air in* a *a typical normal subject and* b *a patient with rectal prolapse. Channels 1–6 represent ports situated 0·5, 1·0, 1·5, 2·0, 2·5 and 4·5 cm from the anal margin. Patients with rectal prolapse showed abnormally low anal pressures before rectal distension, and during rectal distension they showed a prolonged increase in anal pressure caused by increased activity in the external anal sphincter, repetitive rectal contractions and greater rectal sensitivity. The bars* (⊔) *indicate when subjects experienced rectal sensations. DD, desire to defaecate,* +, ++ *and* +++ *indicate the severity of the sensation. EMG, electromyogram*

highest anal pressure always remained above the highest rectal pressure during rectal distension in normal subjects, but was consistently lower than rectal pressures at all volumes of distension in patients with rectal prolapse and became lower in patients with anterior mucosal prolapse and solitary rectal ulcer as the rectal volume increased (*Figure 4*).

Sixty-four per cent of patients with solitary rectal ulcer, 75 per cent with anterior mucosal prolapse, 76 per cent with rectal prolapse, but only 10 per cent of normal volunteers ($P<0{\cdot}05$), showed repetitive rectal contractions during rectal distension (*Figure 2b*).

The differences in the responses to rectal distension between men with solitary rectal ulcer and men in the control group were similar in all respects to those seen between women with solitary rectal ulcer and women in the control group.

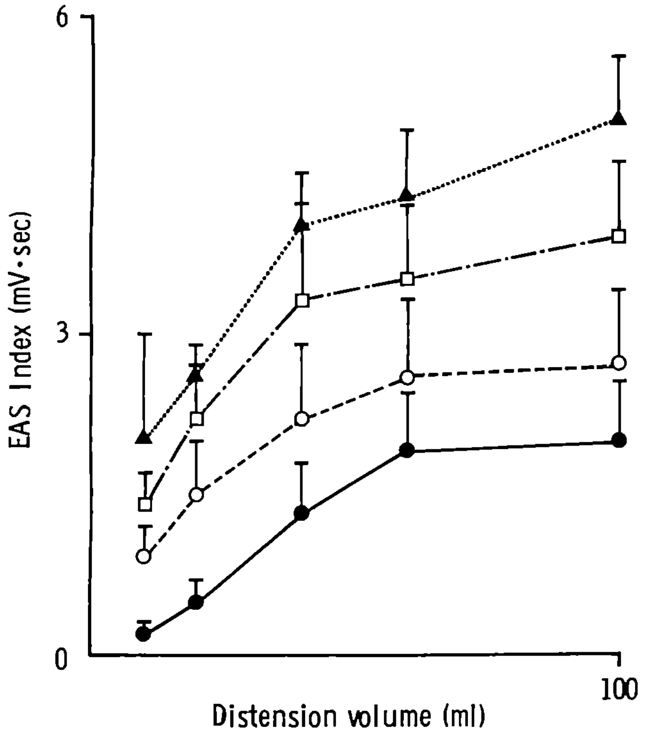

Figure 3 *External anal sphincter index during inflation of a rectal balloon with volumes of 10–100 ml in patients with solitary rectal ulcer (▲), anterior mucosal prolapse (□) and rectal prolapse (○), and in normal subjects (●). External anal sphincter indices were significantly higher ($P<0{\cdot}05$) in patients with solitary rectal ulcer and anterior mucosal prolapse at all volumes of distensions, and in patients with rectal prolapse at 10 and 20 ml Results are shown as mean ±s e m.*

Rectal sensitivity

The distending volume at which the rectal balloon was first perceived and at which subjects complained of a feeling of wind were not significantly different between the groups. The lowest volume required to cause a desire to defaecate and the maximum tolerable volume, however, were significantly higher in normal subjects than in patients, but there were no significant differences in these values between the patient groups (*Table 2*).

Anorectal changes during increases in intra-abdominal pressure

When normal subjects increased their intra-abdominal pressure by blowing up a balloon, this was accompanied by increases in

Table 1 *Highest anal pressures at 100 ml rectal distension*

Anal pressure (cmH_2O)	NS	SRU	AMP	RP
Preinflation	48±4	34±2*	32±3*	14±1*
Residual	25±5	10±3*	22±2	18±2
Rebound	61±6	41±5*	40±3*	19±2*

Data are expressed as mean ±s e m.; NS, normal subjects; SRU, solitary rectal ulcer; AMP, anterior mucosal prolapse; RP, full thickness rectal prolapse, * $P<0{\cdot}05$, significantly different from NS

Table 2 *Rectal sensitivity to rectal distension*

	Lowest rectal volume for different sensation (ml)			
Rectal sensation	NS	SRU	AMP	RP
Perception	12±1	14±1	14±1	14±1
Wind	29±5	18±2	23±4	16±5
Desire to defaecate	53±5	28±3*	37±3*	29±4*
Pain	100±0†	68±6*	83±4*	58±3*

Data are expressed as mean ±s.e.m.; NS, normal subjects; SRU, solitary rectal ulcer; AMP, anterior mucosal prolapse, RP, full thickness rectal prolapse, * $P<0{\cdot}05$, significantly different from NS, † three NS did not feel pain at 100 ml. The highest distension volume (100 ml) was then considered as maximum tolerable volume (pain)

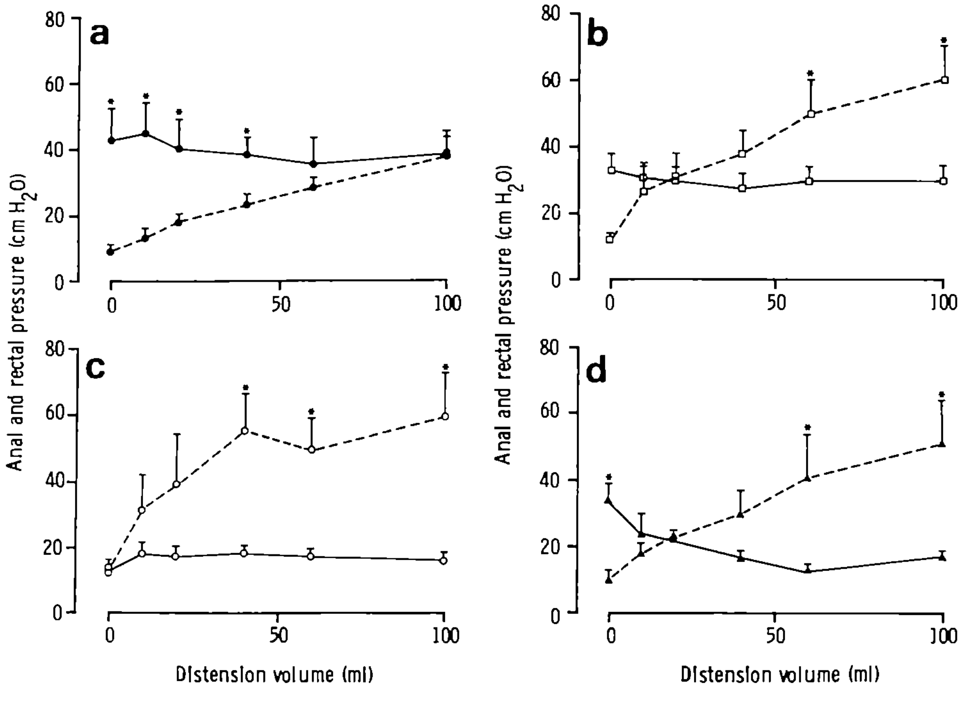

Figure 4 *The highest anal (——) and rectal (– – –) pressures during rectal distension in* **a** *normal subjects and in patients with* **b** *anterior mucosal prolapse,* **c** *rectal prolapse and* **d** *solitary rectal ulcer. Anal pressures always remained above ($P<0{\cdot}05$) rectal pressures in normal subjects, were consistently lower ($P<0{\cdot}05$) than rectal pressures in patients with rectal prolapse, and became lower as the rectal volume increased in patients with anterior mucosal prolapse and solitary rectal ulcer Results are expressed as mean ±s e.m. * Significant difference between anal and rectal pressure ($P<0{\cdot}05$)*

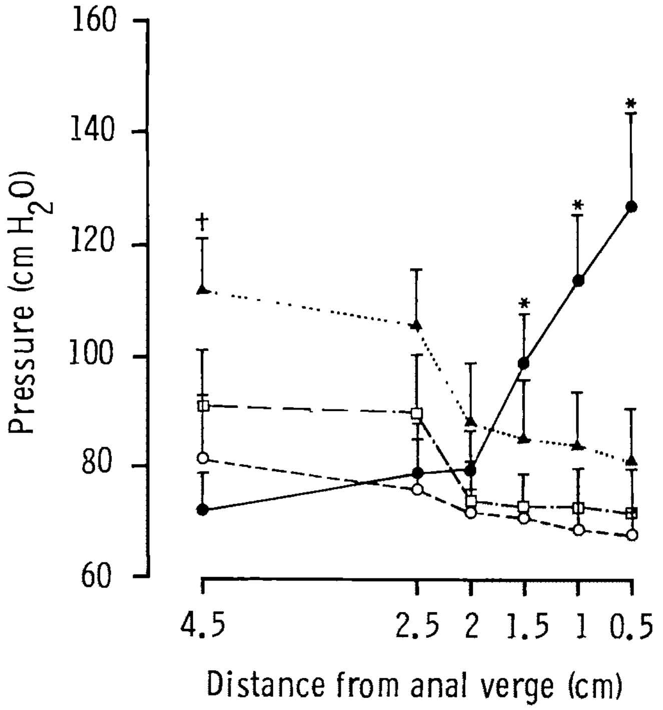

Figure 5 *The highest pressures in the rectum (4·5 cm from the anal verge) and the anal canal when normal subjects (●), patients with solitary rectal ulcer (▲), anterior mucosal prolapse (□) and rectal prolapse (○) increased their intra-abdominal pressure by inflating a balloon Results are expressed as mean ±s e m *Anal pressure was higher in normal subjects than in each of the patient groups* ($P<0{\cdot}001$) *† Rectal pressure in patients with solitary rectal ulcer was higher than in normal subjects* ($P<0{\cdot}05$)

rectal pressure, anal pressures and in the electrical activity in the external anal sphincter The pressures in the more distal anal canal in normal subjects during increases in intra-abdominal pressures were always higher than the rectal pressure (*Figure 5*). Patients with rectal prolapse, solitary rectal ulcer and anterior mucosal prolapse showed similar increases in rectal pressure during increases in intra-abdominal pressure and all demonstrated increased electrical activity of the external sphincter. However, their anal pressures during this manoeuvre were much lower than in normal subjects particularly in the more distal anal channels (*Figure 5*) ($P<0{\cdot}001$), and remained below rectal pressure ($P<0{\cdot}05$), creating in every patient a pressure gradient that would favour incontinence or prolapse The rectal pressure in patients with solitary rectal ulcer was significantly higher ($P<0{\cdot}05$) than in normal subjects and patients with rectal prolapse Men with solitary rectal ulcer also showed the same pattern with lower anal pressures (163 cmH_2O and 87 cmH_2O, normal range 138–367 cmH_2O) and higher rectal pressures (184 cmH_2O and 155 cmH_2O, normal range 52–152 cmH_2O) than in the control group

None of the normal subjects leaked fluid or faeces when they strained to blow up the balloon In contrast, 61 per cent (33 per cent solitary rectal ulcer, 46 per cent anterior mucosal prolapse, 90 per cent rectal prolapse) of the patients leaked, and when this occurred the rectal pressure was always higher than the highest anal pressure.

Discussion

These studies have shown that the anal pressures in patients with full thickness rectal prolapse, anterior mucosal prolapse and solitary rectal ulcer are much lower than in normal subjects Both basal and squeeze pressures are abnormally low, suggesting weakness in both the external and internal sphincters in these conditions. The weakness of the internal sphincter is particularly obvious in patients with rectal prolapse (full thickness rectal prolapse or anterior mucosal prolapse) who have very low anal pressures before and after rectal distension and no anal relaxation. The weakness of the sphincter could explain why so many patients with anterior mucosal prolapse and rectal prolapse suffer from faecal incontinence[19,20].

When normal subjects increased their intra-abdominal pressure in order to blow up a balloon, a compensatory increase in external sphincter activity was associated with a rise in anal pressure above the rectal pressure, creating a pressure barrier that preserved continence. Indeed no leakage of the fluid, infused via the manometric channels, was observed in normal subjects during rises in intra-abdominal pressure. A similar increase in the electrical activity of the external sphincter occurred in all three patient groups during increases in intra-abdominal pressure, and this was greater than that seen in normal subjects, confirming recent data from Womack and colleagues in solitary rectal ulcer patients[21]. However, this enhanced electrical discharge was not associated with higher anal pressures, even though the pressure profile resembled the EMG profile, suggesting it was produced by activity of the external sphincter In fact, the anal pressures did not increase above the rectal pressure in any of the patients, creating conditions that would favour prolapse and incontinence, and caused leakage of infusion fluid during this manoeuvre in 61 per cent of patients. This association between increased electrical discharge and low pressures suggests muscle weakness which may be due to a variety of causes—myopathy, neuropathy or trauma. The observations that these patients all have perineal descent[12,14] and abnormal motor unit potentials[12], however, implicates pudendal neuropathy[11,14] as a major cause of sphincter weakness. Patients with solitary rectal ulcer showed higher rectal pressures during increases in intra-abdominal pressure than patients with prolapse and normal subjects confirming recent observations by Womack *et al.*[21] Thus, we would agree with these authors that solitary rectal ulcer probably represents an early stage in the development of procidentia, where the rectal mucosa prolapses into and plugs the anal canal resulting in higher rectal pressures during straining than in conditions in which the rectum is sufficiently mobile to prolapse out of the anus Womack and his colleagues suggest[21] that ulceration is probably caused by the high transmural pressure gradient in the prolapsing rectum, leading to distension and rupture of submucosal blood vessels and consequent ischaemia of the rectal mucosa[21].

A similar pattern of results was seen in response to rectal distension. All patients showed an increase in external anal sphincter electrical activity in response to rectal distension, and this activity was enhanced in all three groups of patients. The pressures generated during rectal distension, however, were lower than those recorded during the same degrees of distension in normal subjects and, unlike normal subjects, the anal pressures were lower than rectal pressures during rectal distension, creating the conditions for incontinence to occur In addition, the responses to rectal distension indicate enhanced rectal sensitivity and reactivity in all three patient groups Patients perceived the desire to defaecate at much lower volumes than normal subjects and were much more likely to develop rectal contractions in response to rectal distension, causing the rectal pressure to rise above the anal pressure and threatening continence This rectal 'irritability' may in part be secondary to the inflammation caused by prolapse or rectal ulceration and thus similar to the situation found in patients with ulcerative colitis[22] In support of this suggestion, postoperative follow-up studies carried out in one patient whose solitary ulcer had healed showed an increase in the volume required to induce a desire to defaecate and disappearance of the repetitive rectal contractions in response to rectal distension, but no change in the low sphincter pressure.

The increased rectal sensitivity may encourage the subject to attempt to strain when very small volumes are present in the rectum, causing the rectum to prolapse into the weak anal canal. At first only the part of the rectum lying immediately above the anal canal would prolapse (anterior mucosal prolapse), but this may be sufficient to redouble straining efforts[19,23], enhancing the prolapse and exacerbating pelvic floor descent and leading to further neuropathic weakness of the external anal sphincter; this would eventually result in full thickness rectal prolapse. Our observation that the median age of patients with rectal prolapse was two decades later than the median age of patients with solitary rectal ulcer and with anterior mucosal prolapse confirms previous data[24] and would support this proposed development.

In summary, our results suggest that full thickness rectal prolapse, anterior mucosal prolapse, and solitary rectal ulcer may represent different stages of the same basic condition which is associated with a combination of a very weak anal sphincter and an abnormally irritable rectum. The cause of the external sphincter weakness in many of these patients is probably related to pudendal neuropathy, since they all had perineal descent, and previous studies on a similar group of patients showed evidence of reinnervation of the external sphincter, suggesting neuropathic damage to the sphincter[11,12,14,25]. The reason for the concomitant weakness of the internal sphincter is unclear but could possibly be due to traction on the delicate sympathetic nerve supply. The fact that patients in these groups have abnormal descent of the pelvic floor suggests that either failure of the levators to contract and support the pelvic floor during increases in intra-abdominal pressure, and/or stretching and weakness of the connective tissue fascia may initiate the changes in sphincter function observed in this study. Pelvic floor weakness is common after childbirth and this may explain the high female preponderance in this group, although it is important to note that two patients in our group were men and that 15 of the women were nulliparous

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Thigh length versus knee length stockings in the prevention of deep vein thrombosis

M. J. LeF. Porteous, E. A. Nicholson, L. T. Morris, R. James and D. Negus

United Medical and Dental Schools of Guy's and St. Thomas's, Lewisham Hospital, London SE13 6LH, UK

Correspondence to: Mr D. Negus

Above-knee graduated compression stockings are effective in preventing postoperative deep vein thrombosis, but are more expensive and less acceptable than below-knee stockings. One hundred and fourteen patients undergoing major abdominal surgery were randomly allocated to wear above-knee or below-knee graduated compression stockings. Deep vein thromboses were diagnosed by isotope uptake in three of 56 patients (5·4 per cent) in the above-knee group and one of 58 patients (1·7 per cent) in the below-knee group. These differences are not statistically significant. Results suggest that below-knee stockings are as effective as above-knee in the prevention of postoperative deep vein thrombosis.

Keywords: Deep vein thrombosis, ^{125}I-labelled fibrinogen uptake, graduated compression stockings

Effective methods of preventing postoperative deep venous thrombosis include low dose heparin[1,2], low molecular weight dextran[3], intermittent pneumatic compression[4] and graduated compression stockings[5] The latter have the advantages of simplicity, safety and economy.

Wilkins *et al.* (1952) demonstrated that thigh length graduated compression stockings effected a significant reduction in clinically detected pulmonary embolism[6] and, since then, similar stockings have been shown to be effective in reducing the incidence of isotope detected deep vein thrombosis.[7,8]

Knee length (below-knee) stockings are cheaper than thigh length (above-knee) and are more acceptable to patients and nurses, but apart from the study by Tsapogas and his colleagues[9], there has been no previous investigation of their value in preventing postoperative deep vein thrombosis Most deep vein thromboses which follow major abdominal surgery originate in the calf veins[10], and thigh length stockings effect no greater increase in femoral vein blood flow velocity than knee length[11], These observations suggest that knee length stockings will effectively prevent postoperative deep vein thrombosis.

This paper reports the results of a randomized clinical trial comparing the effectiveness of knee length with that of thigh length stockings

Stocking pressures

Lightweight graduated compression stockings (Brevet Hospital Products, Reading, UK) were used throughout the trial. As TED 'Anti Embolism' stockings (Kendall Company (UK) Ltd, London, UK), were used in most previous trials, the pressure profiles of each were compared on healthy volunteers (six legs), using the Borgnis Medical Stocking Tester[12].

Brevet above-knee stockings exerted a higher pressure at the ankle than TED above-knee stockings (Brevet 11 3 mmHg (s.d. ±2·8); TED 9 9 mmHg (s.d ±2·5)), but there was no significant difference in the pressures exerted by each type of stockings at calf or thigh level.

Patients and methods

Informed volunteers over 40 years of age undergoing major abdominal surgery were allocated (by random numbers) to be fitted with above-knee or below-knee Brevet graduated compression stockings on the morning of operation by the same surgical fitter Patients with varicose veins, a past history of deep vein thrombosis or myocardial infarction, premenopausal females and patients undergoing peripheral vascular surgery were excluded.

Stockings were worn until discharge No other method of deep vein thrombosis prophylaxis was used, but leg movement in bed was encouraged, and early mobilization was routine.

Detection of deep vein thrombosis was by ^{125}I-labelled fibrinogen uptake, ^{125}I-labelled fibrinogen was injected intravenously immediately postoperatively and leg scanning was performed on alternate days until discharge Deep vein thrombosis was diagnosed if the count at any point on the leg was 20 per cent greater than adjacent points or the corresponding point on the opposite leg, and if this difference persisted or increased in the subsequent 24 h. (In a previous study ^{125}I-labelled fibrinogen uptake achieved a false positive rate of 7 per cent and a false negative rate of 0 per cent by comparison with phlebography[13]. Phlebography was performed in all but one case with suspected deep vein thrombosis.

Results

One hundred and twenty-four patients were recruited for the trial. Of these, four from the above-knee, and six from the below-knee stocking group were subsequently withdrawn (five ratemeter failures, two inappropriate operations, one patient given heparin, one not fitted with stockings and one unable to tolerate stockings)

One hundred and fourteen patients (56 above-knee and 58 below-knee), were retrospectively matched for the following risk factors sex, malignant disease, cigarette smoking, and pelvic and emergency (i.e. non-elective) surgery, using the χ^2 test, and age, weight, preoperative haemoglobin, duration of anaesthetic, total volume of intravenous saline, time to ambulation and time to discharge, using the *t* test for unmatched pairs (*Table 1*). There was no statistical difference between the groups apart from age and preoperative haemoglobin. The above-knee group were slightly older than the below-knee group and the preoperative haemoglobin was higher in the below-knee group. Both groups of patients underwent similar operations (*Table 2*).

A total of four deep vein thromboses were detected. In the below-knee group calf thrombosis was detected in one patient (1·7 per cent), a 66-year-old woman undergoing emergency laparotomy. This thrombus was clinically overt. Three deep vein thromboses were detected in the above-knee group (5·4 per cent), two were without physical signs, in men aged 75 and 79 years, the former undergoing repair of a large incisional hernia and the latter a cholecystectomy with exploration of the common bile duct for obstructive jaundice. The third patient was a 72-year-old woman undergoing routine cholecystectomy;

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Table 1 *Risk factors in 114 patients*

Risk factor	Above-knee group	Below-knee group	*P*
Male	23	26	n s *
Malignant	20	26	n s *
Smokers	20	17	n.s.*
Pelvic surgery	12	12	n.s.*
Emergency surgery	5	6	n s *
Age (years)	68·0 (11·0)	63·5 (11 2)	<0 05†
Weight (kg)	62 9 (12 3)	67 8 (14·1)	n s †
Preoperative haemoglobin (g/dl)	12·9 (1·7)	13 7 (1 4)	<0 05†
Duration of general anaesthetic (min)	110 (39)	115 (44)	n.s.†
Vol. of IV NaCl (litres)	8 6 (7 5)	8 1 (3·4)	n s †
Time to ambulation (days)	1 5 (0·7)	1 6 (1·3)	n.s †
Total postoperative stay (days)	13 7 (9 4)	13·2 (7·8)	n s †

Mean (s.d) values are given. IV, intravenous; * *P*, calculated using χ^2 test, † *P*, calculated using *t* test for two independent samples

the deep vein thrombosis was clinically overt. There was no statistical difference in the incidence of deep vein thrombosis between the two groups of patients using Fisher's exact probability test. The retrospective exclusion of all patients undergoing emergency surgery, including the one patient in each group who developed a deep vein thrombosis, does not affect this result.

One patient had a superficial thrombophlebitis detected; she was a 70-year-old woman in the above-knee group. Phlebography showed no evidence of deep vein thrombosis.

Below-knee stockings had a number of practical advantages. They were more acceptable than above-knee stockings to patients (especially men), and to the nursing staff. They were also more comfortable and showed no tendency to roll down and produce a garter like band round the leg.

Discussion

These results support the hypothesis derived from the work of Lawrence and Kakkar[11], that above-knee stockings have no advantages over below-knee stockings in the prophylaxis of postoperative deep vein thrombosis.

The deep vein thrombosis rate in these patients was lower than expected; however, three recent studies using above-knee stockings have reported similar or lower rates of deep vein thrombosis[8,14,15], while the only previous work using below-knee stockings, reported a deep vein thrombosis rate of 4 per cent[9].

This study contained too few patients undergoing emergency and pelvic surgery for any conclusions to be drawn from the fact that two of the former and none of the latter group developed a deep vein thrombosis. We recognize that the exclusion of patients undergoing emergency surgery lowers the incidence of deep vein thrombosis in the remaining patients; however, it does not alter the statistical result.

A recent report of two cases of lower limb ischaemia has emphasized the danger of above-knee stockings rolling down and producing a tourniquet effect[16] and suggests that below-knee stockings are safer, particularly in the elderly.

The advantages of patient comfort and safety, and of economy, indicate the need for further large-scale trials to evaluate the place of below-knee graduated compression stockings in the prophylaxis of postoperative deep vein thrombosis.

Table 2 *Operations performed*

Operation	Patients	
	Above-knee	Below-knee
Cholecystectomy	20	14
Colectomy	13	8
Laparotomy	5	6
Gastrectomy	2	9
Rectal operations		
Anterior resection	6	4
Abdominoperineal resection	4	6
Others		11
Total	56	58

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The role of thrombolytic therapy in surgical practice

K. T. Moran,
E. R. Jewell and
A. V. Persson

Section of Peripheral Vascular Surgery, Lahey Clinic Medical Center, 41 Mall Road, Burlington, Massachusetts 01805, USA

Correspondence to:
Dr E. R. Jewell

The ability of streptokinase and urokinase to lyse intravascular fibrin-based clots is firmly established. However, there is a lack of enthusiasm for these agents because of serious haemorrhagic complications and a lack of controlled randomized studies indicating their efficacy. Thrombolytic therapy is suitable in only 15 per cent of patients with acute deep venous thrombosis. It restores the venous circulation to normal in up to 95 per cent of these patients if therapy is instituted within 5 days of the onset of symptoms. These patients have significantly fewer symptoms on follow-up than patients treated with heparin although the ability of thrombolytic therapy to preserve venous valvular function and to prevent the post-phlebitic syndrome is now in question. Thrombolytic therapy is as effective as heparin in preventing pulmonary embolism and may be superior in its treatment. Pulmonary haemodynamics are rapidly improved, diffusion capacity is restored and, although the evidence is inconclusive, long-term pulmonary hypertension may be prevented. Although the mortality rate is not decreased, controlled studies show that thrombolytic therapy may be beneficial in massive pulmonary embolism with clinical shock. Thrombolytic therapy is indicated for acute arterial and acute bypass graft occlusion when the surgical alternative is associated with a higher morbidity and mortality. Partial thrombolysis is achieved in up to 90 per cent of cases and the need for further therapeutic intervention is eliminated in one-third of the patients treated. New thrombolytic agents with greater specificity and potentially greater efficacy and fewer complications are being developed. Tissue plasminogen activator has been successfully used. Prourokinase, fibrin-seeking urokinase and acetylated streptokinase–plasminogen complex may expand the role of thrombolytic therapy in surgical practice.

Keywords: Fibrinolytic therapy, thrombolytic therapy, streptokinase, urokinase, tissue-type plasminogen activator

The role of thrombolytic therapy in surgical practice is controversial with some authors enthusiastically advocating its use while others consider it a therapy 'whose time has passed'[1,2]. In this review we will discuss the clotting mechanism, the fibrinolytic system, the various thrombolytic agents currently available, the indications for thrombolytic therapy, the potential benefits and risks of this therapy, the therapeutic regimens used and the use of adjunctive anticoagulation

The clotting mechanism

The *in vivo* action of the clotting mechanism is balanced by limiting reactions that normally prevent clots from developing in uninjured vessels. When endothelium is disrupted, collagen is exposed attracting platelets which adhere and liberate serotonin and adenosine diphosphate. Platelet aggregation ensues. A temporary loose plug is formed. This is converted into the definitive clot by fibrin in a reaction which requires calcium ions and is catalysed by factor XIII The fundamental reaction in the clotting of blood is conversion of the soluble plasma protein fibrinogen to insoluble fibrin in a reaction catalysed by thrombin. Thrombin is a serine protease that is formed from prothrombin by the action of activated factor X.

Factor X can be activated by reactions that proceed along either an intrinsic or an extrinsic pathway. The initial reaction in the intrinsic pathway is the activation of factor XII when blood is exposed to the collagen fibres underlying the endothelium in blood vessels. Factor XII activates factor XI which activates factor IX. In the presence of factor VIII and platelets, active factor IX activates factor X The extrinsic system involves the activation of factor VII by tissue thromboplastin, a protein–lipid complex released from blood vessel walls and a variety of other tissues when they are damaged. Active factor VII then activates factor X.

The fibrinolytic system

The physiological fibrinolytic system (*Figure 1*) maintains the patency of the circulation by dissolving the fibrin network of arterial and venous thrombi The primary fibrinolytic enzyme plasmin is formed by the activation of plasminogen, a normal circulating constituent of plasma Plasminogen has a strong affinity for fibrin and when intravascular thrombi are formed plasminogen becomes bound to fibrin[3]. During normal physiological fibrinolysis, tissue plasminogen activator is released from vascular endothelium and activates the fibrin-bound plasminogen Release of the plasminogen activator may be achieved by a wide variety of stimuli including venous occlusion, ischaemia, strenuous exercise, emotional stress, surgery, and local or systemic administration of vasoactive agents such as catecholamines, nicotinic acid and vasopressin analogues[4,5]. The result is a selective localized fibrinolysis[3,6,7]. A systemic lytic state is avoided and fibrinogen, prothrombin, factors V and VIII are unchanged[3,6,7]

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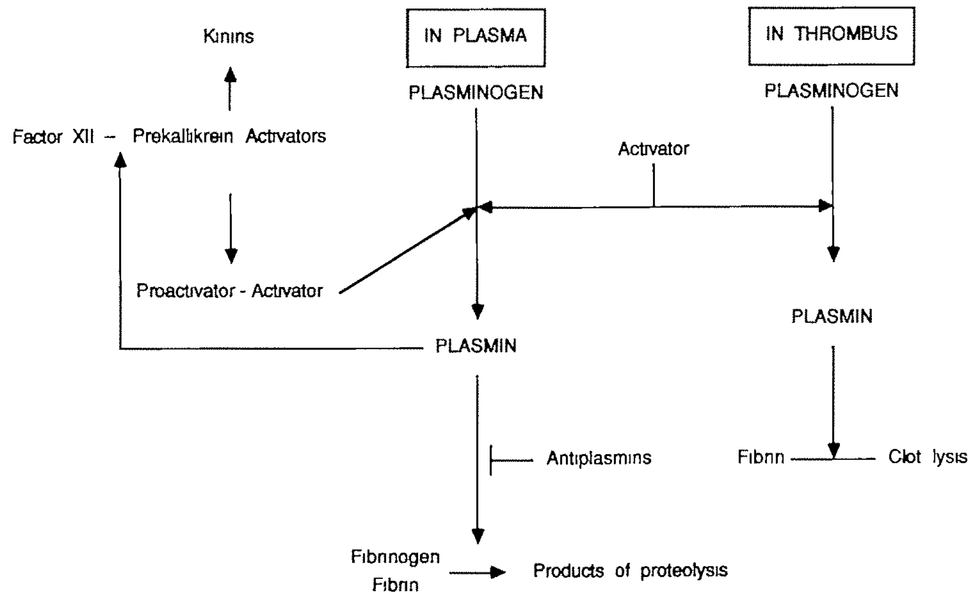

Figure 1 *The fibrinolytic system*

Circulating blood contains a number of inhibitors of fibrinolysis which under physiological conditions maintain a homoeostatic balance with active enzymes. These inhibitors inactivate plasmin once it is formed[8] They include α_1-antitrypsin, α_2-plasmin inhibitor, antithrombin-3 and α_2-macroglobulin Inhibitors of fibrinolysis have also been described in a number of body tissues, particularly platelets. In addition to exhibiting a weak antiplasmin effect, platelets were found to contain inhibitors of plasminogen activators including urokinase[9,10].

Agents that are capable of accelerating the fibrinolytic system are of interest to the surgeon because they have the potential to decrease the morbidity and mortality associated with thrombotic conditions. All agents in clinical use activate plasminogen rather than depolymerize fibrin directly[11]. Plasminogen is available from three sources: (a) trapped in the clot, (b) circulating in the plasma and (c) produced by the liver and entering the circulation after a thrombolytic agent has been administered[11,12].

This has important implications for the use of thrombolytic therapy[11,12]. Injecting the drug directly into a clot would convert only the trapped plasminogen. To create a systemic lytic state the thrombolytic agent must enter the general circulation. When thrombolytic therapy is instituted systemically the lytic agent activates circulating plasminogen. Once all the plasminogen has been converted additional activity depends on further plasminogen production by the liver and activation of the plasminogen in the clot. Thus with a prolonged continuous infusion the activity of the drug depends more on the production of plasminogen by the liver than on the amount of drug administered[11].

Thrombolytic agents

All the thrombolytic agents currently in use or under development act directly or indirectly as plasminogen activators[13]. Streptokinase was discovered in 1933 when it was observed that a filtrate of group C β-haemolytic streptococci lysed a human plasma clot[14]. Urokinase initially isolated from human urine in 1946 is now obtained from tissue culture of human embryonic kidney cells[15]. Urokinase activates plasminogen directly and has a more predictable therapeutic response than streptokinase which forms an equimolar complex with plasminogen or plasmin and this complex activates the remaining plasminogen[16]. Streptokinase must neutralize any streptococcal antibodies present in the circulation before a lytic state can be achieved. Following the administration of streptokinase, antibodies are produced which preclude the use of streptokinase for 1 year. Urokinase is less antigenic and does not have this problem with antibodies. However, urokinase is almost 20 times as expensive as streptokinase for an equivalent therapeutic dose[17].

As both urokinase and streptokinase activate circulating plasminogen, thus depleting plasma plasminogen levels and leading to the degradation of fibrinogen and the other clotting factors, there is a growing interest in 'fibrin-specific' plasminogen activators[13]. Although these agents have a higher ratio of activity for fibrin-bound plasminogen they do activate plasma plasminogen and in therapeutic doses cause systemic fibrinogenolysis[13]. Tissue plasminogen activator is now being made in tissue culture by recombinant DNA techniques utilizing a mammalian cell line. Animal studies and laboratory tests have shown it to be an effective thrombolytic agent[18,19]. Tissue plasminogen activator forms a complex with fibrin and plasminogen. This complex specifically activates plasminogen in the presence of fibrin and should have little effect on circulating plasminogen. Therefore theoretically it should induce local thrombolysis without systemic fibrinolysis. However, studies have shown the same incidence of bleeding episodes among patients treated with tissue plasminogen activator and those treated with streptokinase after myocardial infarction[20]. Further clinical trials are in progress[21,22].

Investigators continue to attempt to improve the specificity and efficiency of streptokinase and urokinase The development of prourokinase[23] and fibrin-seeking urokinase[24] has recently been reported Prourokinase is an inactive proenzyme which is slowly activated in the presence of a fibrin clot Fibrin-seeking urokinase (urokinase coupled with a monoclonal antibody that is fibrin specific and does not cross-react with fibrinogen) has demonstrated a 100-fold increase in *in vitro* fibrinolysis when compared with unmodified urokinase[25]. Selective clot lysis can be achieved by acylating the streptokinase–plasminogen complex to form anisoylated plasminogen–streptokinase activator complex (APSAC). When the complex is bound to fibrin, deacylation occurs and fibrin-bound plasminogen is activated[3,25].

The 'fibrin-selective' agents have been used predominantly after myocardial infarction[13]. Evidence suggests that there is an inverse relationship between the degree of fibrin selectivity and the lytic state achieved[13]. After myocardial infarction, when thrombolytic agents are used in therapeutic doses, the lytic state is greatest with streptokinase and APSAC[20,26], is at an intermediate level with urokinase[27], and is more moderate with prourokinase and tissue plasminogen activator[20,28]. Although relative fibrin specificity is important in the development of a lytic state the plasma half-life of each agent also influences the outcome, with prourokinase and tissue plasminogen activator having a rapid turnover[28,29], streptokinase[30] and urokinase[31] having intermediate rates and APSAC having the slowest rate[32] Rethrombosis after reperfusion occurs in roughly inverse proportion to the length of plasma half-life with the lowest incidence following APSAC[26,32], urokinase[27], and streptokinase[33], and the highest following tissue plasminogen activator[33,34]. These findings, in patients after myocardial infarction, may have important implications for surgical practice.

Indications for fibrinolytic therapy

The major indications for fibrinolytic therapy are deep venous thrombosis, pulmonary embolism, occlusion of native arteries, occlusion of venous or prosthetic grafts, and thrombosis of renal dialysis sites (shunts, fistulae and interposition grafts). Anecdotal reports of successful management of thrombosed coeliac, superior mesenteric and renal arteries with regional fibrinolytic therapy exist[35-37]. However, visceral artery occlusion is not a common indication because of the inability of these organs to tolerate prolonged ischaemia.

Contraindications for fibrinolytic therapy

Fibrinolytic therapy is contraindicated for 10 days after surgical procedures and parturition and for 3 months after the insertion of a vascular graft. Other contraindications include a bleeding diathesis, blood dyscrasias, liver disease, recent cerebrovascular accident or gastrointestinal haemorrhage. Although thrombolytic agents have been successfully used intraoperatively[38,39] to lyse residual thrombus following thromboembolectomy, more information is required before this can be regarded as an indication. Meanwhile recent surgery remains an absolute contraindication.

Therapeutic regimens

There are three commonly used regimens for administering thrombolytic agents. The commonest method is the continuous infusion of a thrombolytic agent into either a peripheral or central vein. Streptokinase is administered in an initial dose of 250 000 units over the first hour and 100 000 units every hour for the duration of therapy. Urokinase is administered in an initial dose of 4400 units kg^{-1} over 30 min and 4400 units $kg^{-1} h^{-1}$ for the course of therapy Duration of therapy is determined by the clinical response and is usually 72–96 h.

The second regimen is the infusion of a low dose of the thrombolytic agent directly into the clotted vessel. This method was introduced in the hope of increasing the rate of fibrinolysis and decreasing the systemic lytic effects and other complications[40,41]. A catheter is placed with its tip at the site of the occlusion Streptokinase in a dose of 5000–10 000 units h^{-1} or urokinase in a dose of 20 000–40 000 units h^{-1} is infused. Treatment times vary from 12 to 72 h depending on the clinical response

A third regimen which uses streptokinase or urokinase in an intermittent dosage schedule has been called 'burst' therapy[42,43]. Using this regimen 250 000 units streptokinase or 4400 units kg^{-1} urokinase is infused during the first hour of therapy This is followed by 100 000 units h^{-1} streptokinase or 4400 units urkinase $kg^{-1} h^{-1}$, for 4 h. The infusion is then discontinued for 12 h to allow the liver to replenish the circulating plasminogen. After this, 100 000 units streptokinase or 4400 units kg^{-1} urokinase is given over a 1-h period twice daily for 4–6 days. The duration of therapy is dictated by the patient's response.

A fourth regimen significantly reduces mortality following myocardial infarction and may be potentially useful for evaluation in peripheral arterial and venous thrombosis. In this regimen a bolus of streptokinase ($1{\cdot}5 \times 10^6$ units) is infused over 1 h[13]

Monitoring during therapy

Before commencing therapy a partial thromboplastin time, prothrombin time, haematocrit, fibrinogen level and platelet count are usually obtained to screen for a coagulopathy. Laboratory monitoring does not accurately predict the likelihood of bleeding or of successful clot lysis[44] All patients should be carefully monitored but it has been shown that it is not necessary to confine them to the intensive care unit[42]. Determination of a partial thromboplastin time and fibrinogen levels 3 h after commencing therapy will indicate if a lytic state has been achieved. The therapeutic effect of thrombolytic therapy is most accurately determined by serial angiography or non-invasive methods[42].

Deep venous thrombosis

The therapeutic objectives of therapy in deep venous thrombosis are the promotion of thrombus resolution and the restoration of normal venous circulation in the affected veins thus relieving symptoms and preventing the post-phlebitic syndrome All goals of treatment may be achieved by using thrombolytic therapy[45]

It has been reported that only 15 per cent of patients with deep venous thrombosis are candidates for thrombolytic therapy[46] The majority of patients have a contraindication such as recent surgery. The size and location of the clot, the underlying risk factors for deep venous thrombosis and the particular fibrinolytic agent used do not seem to alter the outcome of therapy[47]. Patients with iliofemoral thrombosis and impending venous gangrene are particularly suitable and thrombi in veins draining the upper extremities have also been reported to respond favourably[48,49] However, in those patients suitable for thrombolytic therapy it is inappropriate to begin heparin therapy and then to change to thrombolytic agents after 2 or 3 days because the chance of successful lysis is decreased by 50 per cent[50]. Randomized studies comparing streptokinase and heparin in the treatment of deep vein thrombosis have shown that clot lysis was significantly more likely with streptokinase but there was also a higher incidence of haemorrhagic complications[51] with this agent.

Restoration of the venous system to normal is achieved in 90–95 per cent of patients if thrombolytic therapy is administered within 5–7 days of the onset of symptoms[52-54] Results are less favourable if thrombosis has been present for more than 5 days The venous system will return to normal in less than 50 per cent of these patients[50]. After 10 days of symptoms, only 10–15 per cent of patients receive benefit from thrombolytic therapy[45].

In long-term follow-up studies, 77 per cent of patients with popliteal, femoral, or iliofemoral thrombosis treated with anticoagulants alone remained symptomatic[55]. In other prospective studies comparing streptokinase and heparin therapy for similar indications, there were significantly fewer symptomatic patients in the streptokinase-treated groups[52,56,57]. Streptokinase is as effective as heparin in preventing pulmonary emboli[58]. Kakkar *et al.*[59] showed that normal venous valvular function was maintained for 6–12 months in 47 patients treated with streptokinase However, subsequent studies by the same authors showed the same degree of haemodynamic impairment over a 2-year period in two groups of patients, irrespective of whether they were treated with heparin or with streptokinase[60]. With regard to the ability of streptokinase therapy to prevent late post-thrombotic changes in the affected limb, the evidence is equally confusing. Arnesen *et al.*[52] suggest that streptokinase is effective in preventing late post-thrombotic changes while Kakkar and Lawrence[60] have produced evidence to the contrary.

Pulmonary embolus

Thrombolytic agents combined with heparin have been shown to be superior to heparin alone in the management of pulmonary embolus[58]. These patients had a more rapid improvement in abnormal perfusion lung scans and elevated pulmonary artery pressures than did patients who received heparin alone. The difference in physiological response was specially evident in patients with massive pulmonary embolism (more than two lobar arteries involved) and symptoms for less than 48 h and could be achieved equally well with streptokinase or urokinase. Similar effects have been demonstrated with tissue plasminogen activator[61,62]. Other studies have revealed that thrombolytic therapy achieved earlier lysis of the clot and a more rapid improvement in pulmonary haemodynamics[3,6,63,64]. In addition, thrombolytic agents may restore diffusion capacity and prevent pulmonary hypertension[3,6,64]

However, the evidence for a lasting advantage of thrombolytic therapy over heparin therapy alone is as yet inconclusive. In the Urokinase–Streptokinase Pulmonary Embolism Trial there was no difference in mortality rates between patients treated with heparin and those treated with thrombolytic agents[58] although in a subgroup in this study mortality was lower with urokinase therapy than after emergency pulmonary embolectomy. Percutaneous transvenous embolectomy with a suction device that allows withdrawal of thrombus from the main pulmonary arteries has not received widespread acceptance and there is insufficient information available to compare this modality with thrombolytic therapy[65]. In other randomized studies in patients with massive embolism and clinical shock, reperfusion was more successful after thrombolytic therapy[66,67]. Thus, unless contraindicated by a lifethreatening risk of haemorrhage, thrombolytic therapy appears to be the treatment of choice for pulmonary embolism with acute pulmonary hypertension, shock responding to medical treatment, and complete perfusion defects involving one or more lobes[3].

Evidence from animal experiments suggests that clot is more rapidly lysed when fibrinolytic agents are infused directly into the thrombus[7]. The next most rapid lysis occurred with infusion into the pulmonary artery while peripheral venous infusion was least efficient[68]. These animal studies are corroborated by recent clinical studies[63].

Peripheral vascular disease

Thrombolytic therapy has been used in a variety of arterial occlusive processes including upper and lower limb ischaemia, occlusion of bypass grafts and thrombosis after percutaneous transluminal angioplasty[69,70] Selection of patients for thrombolytic therapy depends on a number of factors including the general condition of the patient, the severity and duration of the ischaemia and the underlying cause[71]

As a rule, thrombolytic therapy should be considered when the morbidity and mortality associated with the surgical alternative are higher than the anticipated incidence of serious haemorrhagic complications associated with therapy Such high risk patients include patients after myocardial infarction, those with lower limb ischaemia, thrombosis of a popliteal aneurysm, emboli to distal muscular arteries or surgically inaccessible vessels, and those with diffuse thrombosis[71,72]. As surgical results are generally poor and the amputation rate is high with occlusion of the popliteal or tibial vessels, even good-risk patients may be candidates for thrombolytic therapy. Patients with the blue toe syndrome (occlusion of the digital arteries) and trash foot (distal embolization following arterial surgery) may also be candidates for thrombolytic therapy[50]. Thrombolytic agents are contraindicated if the acute ischaemia has resulted in a neurological deficit, i.e. numbness and/or paraesthesia. It is also inappropriate in patients who cannot tolerate the ischaemia during the infusion period. Although it is desirable to differentiate between embolus and thrombosis, this is frequently impossible. Emboli can be lysed in up to 80 per cent of cases while thrombolytic occlusions have been reported to be lysed in 50–60 per cent of cases[41,73,74]. Intraoperative infusion of lytic agents has been used successfully after thromboembolectomy in patients where arteriography demonstrated residual thrombus distal to the popliteal artery. There were no complications related to the infusions[38,39].

The incidence of successful thrombolysis in acute arterial and bypass graft occlusion is very variable (30–90 per cent (*Table 1*)). Occluded arteries and bypass grafts were initially treated by systemic thrombolytic administration but the increased efficacy of local therapy has been recognized, particularly for bypass grafts[25,40–44]. It has been shown that the fibrinolytic effect is magnified if the agent is injected directly into the clotted graft Improved results are also reported if a passageway is made by means of a catheter or guidewire, although there may be a higher incidence of vessel dissection and peripheral embolism[86,87]. The greatest potential benefit from thrombolytic treatment is in patients with occluded autogenous vein grafts[71]. Restoration of flow in an occluded graft permits complete angiographic evaluation of the graft and may identify the cause of the graft failure, which can then be corrected. Indeed, two-thirds of all patients with acute arterial or bypass graft occlusions that respond to thrombolytic therapy require further therapeutic intervention[73,75,88].

Thrombosed catheters, dialysis shunts and arteriovenous fistulae

Central venous catheters can be cleared by injecting a small quantity of concentrated streptokinase solution (250 000 units in 2 ml) to fill the lumen. After 1 h the catheter is aspirated and flushed[3]. Fibrinolytic agents are more effective in clearing dialysis shunts than arteriovenous fistulae[89,90]. However, the risk of haemorrhagic complications in this group is high[91].

Adjunctive anticoagulation

There is a higher incidence of haemorrhagic complications where thrombolytic agents and anticoagulants are administered simultaneously[44]. However, there is debate about whether concomitant anticoagulation with heparin should be used during the local infusion of fibrinolytic agents for arterial occlusion. Some authors believe that anticoagulation causes a reduction in rethrombosis around the catheter as thrombolysis progresses more distally[1,77], while others believe it is an unnecessary hazard[70]. The low flow, low pressure characteristics of the venous system predispose to rethrombosis following thrombolytic therapy if anticoagulants are not used[25]. Heparin may be administered for 1 week followed by an oral anticoagulant (coumarin) for 3 months[16]. 'Burst' therapy has been shown to decrease hospital time and to be more cost-effective[42]. Administering coumarin the evening before the last dose of streptokinase markedly reduces the time required to anticoagulate the patient[42] adequately.

Discussion

It is unlikely that there will ever be an ideal thrombolytic agent, i e one that is non-antigenic, inexpensive, selectively dissolves thrombus and that acts quickly, completely and without complications. It is probable that there will always be an increased risk of bleeding because it is difficult to conceive of any agent dissolving the fibrin of an intravascular clot while not dissolving the fibrin of a haemostatic plug. However, the thrombolytic agents currently used in surgical practice or following myocardial infarction (streptokinase, urokinase, tissue plasminogen activator, prourokinase and APSAC) can be improved. Fibrin specificity can be improved by complexing any of these agents with a monoclonal antifibrin antibody[92]. A disadvantage of streptokinase and APSAC is their antigenicity, which limits their use in retreatment as well as exposing

Table 1 *Reported success rates using thrombolytic therapy in vessel and bypass graft occlusion*

		Successful lysis/total attempted				
Reference	Thrombolytic agent	Artery	Vein	Prosthetic graft	Success rate (%)	Haemorrhagic complications (%)
1982						
Hargrove *et al*[70]	S	8/8	4/6	1/2	81	37
Hess *et al.*[75]	S	70/136			51	3
1983						
Berni *et al*[73]	S	10/12	2/2	1/2	81	25
1984						
Dardik *et al.*[76]	S	9/9	8/26		49	9
Wolfson *et al*[77]	S	11/18	7/9		67	4
Katzen *et al*[78]	S	44/55		7/10	78	9
1985						
Sicard *et al*[79]	S/U	13/29	3/14*		37	18
Hallett *et al*[80]	S/U	13/20	6/18*		50	14
Graor *et al.*[69]	S	25/45	8/13	19/27	61	12
Goldberg *et al*[81]	S			9/10	90	60
Kakkasseril *et al*[82]	S	7/14	5/5	3/16	43	37
Perler *et al*[2]	S/U		3/6	0/4	30	10
1986						
Ferguson *et al.*[83]	S	54/65	10/14	15/23	77	11
Hamelink and Elliott[84]	S	23/34		4/11	60	38
Belkin *et al.*[85]	S/U	16/22	1/2	5/8	69	48
Graor *et al*[22]	tPA	10/12	3/3	2/3	83	0

S, streptokinase; U, urokinase, tPA, tissue plasminogen activator; * vein and prosthetic graft

patients to an increased risk of allergic reactions. Streptokinase and APSAC have been reported to lose their antigenicity following treatment with polyethylene glycol[93] The short half-life of most of these agents (tissue plasminogen activator, 5 min, prourokinase, 7 min; urokinase, 16 min; streptokinase, 23 min) usually requires their administration in large amounts over a long period. Techniques for prolonging the half-lives of these agents are being developed[94] This may be achieved by acylation of the active enzyme centre as in APSAC or by pharmacologically altering the mechanisms for their inactivation[95]. The potential for combining thrombolytic agents needs to be explored Tissue plasminogen activator and urokinase have been shown to act synergistically, significantly reducing the amount of each needed to effect clot lysis[96]. Recombinant DNA techniques which can create unique molecules with altered domains and susceptibility to plasmin clearance will be used to create new thrombolytic agents. The cost of thrombolytic therapy will be an important consideration with regard to both the initial purchase price and the cost of caring for patients with thrombotic disease[14] Although expensive, thrombolytic therapy will probably become more cost-effective by decreasing the length of hospital stay and reducing the need for emergency surgery

For the moment thrombolytic therapy affords the possibility of removing intravascular thrombi before irreversible tissue damage or organ failure occurs In contrast anticoagulant therapy merely prevents extension of the thrombotic process The lack of enthusiasm for thrombolytic therapy is attributed to two factors[71]: firstly, the perceived high risk of serious haemorrhage and other systemic complications and, secondly, the paucity of controlled randomized clinical trials documenting the efficacy of treatment.

It is difficult to determine the incidence of significant haemorrhagic complications because there are no standard criteria for assessing these complications. The incidence in reported series varies from zero to 60 per cent (*Table 1*). In the Urokinase–Streptokinase Pulmonary Embolism Trial, the incidence of bleeding requiring transfusion of 1 or more units of blood varied from 13 to 18 per cent[58]. The incidence of systemic haemorrhagic complications varies with the method of thrombolytic administration. It is highest with intravenous use and is reduced by local catheter administration[1,71]. However, with the latter method, haemorrhage around the catheter site is significant[69], occurring in 20 per cent of patients in one series[97]. In addition, even with local infusion a systemic lytic state develops within 12–24 h and major or minor haemorrhagic complications occur in 15–30 per cent of patients[25]. The duration of therapy directly influences the incidence of haemorrhagic complications[44]. Partial thrombolysis should be apparent within 24 h and continuing therapy without evidence of beneficial effect beyond 48–72 h seldom yields a more favourable outcome[1]. With prosthetic grafts (Dacron® (E I. du Pont de Nemours and Company) and less commonly polytetrafluoroethylene) the fibrin in the interstices may be digested, resulting in significant bleeding[98]. The choice of agent may also be important. Urokinase and tissue plasminogen activator have been reported to be associated with a lower incidence of haemorrhage than has streptokinase[1,19,85]. Tissue plasminogen activator has been reported to lyse pulmonary emboli more effectively than urokinase[62] However, there is as yet no evidence from large randomized studies to support these reports. Cerebrovascular haemorrhage, the most dreaded of all complications, has been reported in 2·2 per cent of cases[99].

Comparison of success rates in various series (*Table 1*) is difficult owing to the many factors that may influence the outcome, e.g the thrombolytic agent chosen, the technique of administration, the dosage regimen used and the selection of patients. Some general observations can be made. Acute occlusions respond better than chronic occlusions and short occlusions better than longer segments. Urokinase may be more effective than streptokinase. With the use of local low dose therapy, bypass graft may now respond as rapidly as native vessels. In selecting patients for fibrinolytic therapy, careful clinical assessment and consideration of clinical alternatives are necessary to minimize the risks and maximize the benefits.

In conclusion, fibrinolytic therapy has a definite role in surgical practice. This role may be expanded by the greater specificity of tissue plasminogen activator and by agents such as prourokinase, fibrin-seeking urokinase and APSAC which are currently being investigated. All of these agents can be improved, and recombinant DNA technology will be used to develop new agents. Newer non-invasive techniques provide the opportunity to study their effects during therapy and subsequently over a period of time.

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Professor of Pathology, The George Washington University, School of Medicine, Washington DC, USA.

- ★ **Clearly and concisely written with extensive illustrations including many in colour**
- ★ **Cover all the aspects of the technique from performance to evaluation**
- ★ **Essential reading for surgical pathologists involved in performing aspirations**

Fine needle aspiration is a valuable diagnostic tool that is gaining increased acceptance in the United States. It helps clinicians and surgeons arrive at a more accurate diagnosis in a timely and economical fashion and enhances their ability to manage patients more effectively. This monograph is the product of nine years' experience in which about 10,000 aspirates were interpreted or performed. It covers all aspects of the technique, from performance of the aspiration and processing the specimen, to the evaluation of the information obtained from the procedure. As this experience has shown that results are superior when the aspiration is performed by the pathologist, the emphasis throughout is on the technical aspects of the procedure. The text is extremely well illustrated to facilitate evaluation and differentiation of findings. The result is a clearly written, practical guide to fine needle aspiration of the breast.

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Role of B-mode venous mapping in infrainguinal in situ vein–arterial bypasses

P. W. Leopold,
A. Shandall,
A. M. Kupinkski,
B. B. Chang, J. Kaufman,
D. M. Shah and
R. P. Leather

Vascular Surgery Section,
Department of Surgery, Albany
Medical College, Albany, New York
12208, USA
Correspondence to:
Mr P W Leopold

Two hundred and eighty patients underwent B-mode mapping (B-map) of their saphenous vein over a period of 3 years (1984–1987) before lower limb revascularization. B-map deemed that 229 veins were suitable for bypass, 26 were questionable and 25 were unsuitable. A successful bypass was achieved in 97·8 per cent of the suitable group (all in situ*), 85 per cent of the questionable group (*in situ *and composite vein), and 80 per cent of the unsuitable group (composite vein). At a minimum follow-up period of 1 year the overall patency rate was 95·0 per cent with a revision rate of 15·8 per cent. There was no correlation between revision rate and vein complexity or calf vein diameter. Calf vein diameter >2·5 mm was correlated with a successful bypass (*$P<0{\cdot}001$*). It is concluded that B-map is the investigation of choice for saphenous vein assessment before infrainguinal bypass surgery.*

Keywords: Ultrasound, B-mode, infrainguinal bypass, saphenous vein

Autogenous saphenous vein, whether *in situ*, reversed, or composite, has been proved to be the best available conduit for infrainguinal arterial reconstruction[1–3]. Many authors now feel that, where possible, the *in situ* saphenous vein bypass offers the best surgical option[4].

The *in situ* bypass may be performed using techniques of either partial or complete saphenous vein exposure. We have preferred the technique of partial vein exposure to reduce skin flap necrosis, increase speed of surgery, and reduce operative time[5]. Under these circumstances we have found it essential to have a full and detailed knowledge of the saphenous venous anatomy particularly in the unexposed thigh section of the saphenous vein. Pre-bypass venography has been used by ourselves and others to determine saphenous vein anatomy[6,7]. Some authors have warned against the use of saphenous veins other than single systems for vein bypass surgery. This approach would lead to a vein utilization rate as low as 60 per cent. Our experience with pre-bypass venography was associated with a vein utilization rate of 95 per cent. With the development of B-mode imaging, a further technique became available to preoperatively assess the greater saphenous vein. Our initial trial of preoperative venography against B-mode mapping (B-map) in 50 consecutive patients was favourable, suggesting the use of B-map as an independent technique with certain guidelines[9]. Since then others have published their initial experience with superficial venous imaging[10]

The aim of this study was to determine: firstly, whether B-map adequately assessed the saphenous vein, achieving similar vein utilization rates as venography; secondly, whether vein diameter and complexity of the venous system affected the outcome; and lastly, whether there was any advantage of B-map over venography in terms of anatomical three-dimensional detail and the facilitation of better infrainguinal bypass technique, avoiding the complications previously ascribed to partial vein exposure.

Patients and methods

Two hundred and eighty consecutive patients underwent B-map of their saphenous veins between 1984 and 1987. All these patients presented with limb-threatening ischaemia[11] The mean age was 67·5 years with a male preponderance (65 per cent), 48 per cent of patients were diabetic and 67 per cent were smokers

B-mode mapping (B-map)

All patients were examined in a position of 20° reverse Trendelenberg tilt as previously described. Starting at the knee joint the saphenous vein was visualized using a Diasonics DRF 400 Duplex scanner (Sonatron Ltd , Bedford, UK), utilizing a 10 MHz imager The cross-sectional scan was used to measure the venous diameter, and the vein path along the limb was marked from the longitudinal scan The main trunk was followed from the knee proximally and distally, marking (1) the path, (2) the diameter, (3) the cutaneous and deep branches and (4) double/triple/more complex systems. A full-length map of the saphenous system including, if necessary, the short saphenous system was marked on the leg The internal diameter of the vein was recorded in the proximal and distal thigh regions and at the knee and ankle levels. A re-examination was performed in the standing position, if the patient's condition allowed, to ensure adequate venous filling Patients with complex systems and inadequate B-map examinations underwent venography, at the discretion of the clinician

Results

Two hundred and twenty-nine veins were deemed suitable for bypass, 26 were questionable (< 2·5 mm at the calf but complete and patent), and 25 were unsuitable (incomplete, previously excised, damaged or diseased)

A successful bypass was achieved in 97 8 per cent of the suitable vein group (all *in situ*), 85 per cent of the questionable group (*in situ* plus composite vein) and 80 per cent of the unsuitable group (composite vein, *Figure 1*). In 23 patients (out of the 51 questionable or unsuitable) branches of the long or short saphenous were used for composite vein grafting or short saphenous *in situ* bypass (*Table 1*); 34 per cent of the bypasses were to the popliteal level and 66 per cent were infrapopliteal.

Patients were followed up at 1 month and then at 3-monthly intervals. This included a symptomatic enquiry, clinical examination and vascular laboratory studies, including pulse volume recording and Duplex scanning of the bypass.

There was a minimum follow-up period of 1 year for all bypasses resulting in a secondary patency rate of 95 per cent[11]. The revision rate was 15·8 per cent (42/266) An analysis of vein complexity in the thigh (double, triple or branching systems), and revision rate showed no statistical difference (*Table 2*). Also an analysis of calf vein diameter and revision rate showed no

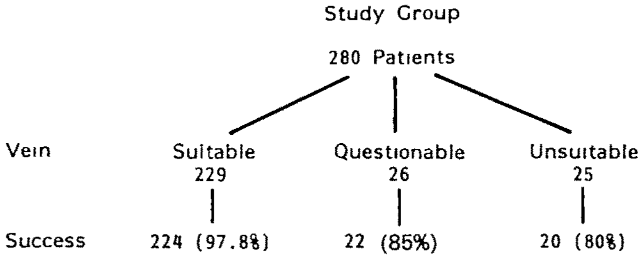

Figure 1 *The result of the B-map studies in 280 patients in relationship to the outcome of the surgical procedure*

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Table 1 *Alternative veins (composite bypasses) used in 23 patients*

Femoropopliteal	9
Femorodistal	7
Vein patch	4
Short saphenous *in situ*	3

Table 2 *Vein complexity and revisions*

	Revisions	Non-revisions	Total
Complex	17	99	116
Non-complex	25	125	150
Total	42	224	266

$\chi^2 = 0{\cdot}19$, n.s

Table 3 *B-mode vein diameter*

Position	Mean ± s.d. (mm)
Proximal thigh	4·360 ± 1 050
Distal thigh	3 660 ± 0 900
Knee	3·383 ± 0·925
Calf	2·834 ± 0·731*
Ankle	3·040 ± 0 756*

* Significant difference $t = 2{\cdot}482$, $P < 0{\cdot}02$

statistical difference. (Revised bypass calf diameter in millimetres, 2·86 ± 0 71, $n = 42$; non-revised 2·76 ± 0 21, $n = 224$ (mean ± s.d.); *t* test n.s.) However, comparing the calf vein diameter above and below 2·5 mm showed a significant difference in the feasibility of a successful bypass (<2 5 mm, 19/29; >2·5 mm, 224/229; $\chi^2 = 49{\cdot}04$, $P < 0{\cdot}001$).

It is interesting to note that the saphenous vein diameter decreased from groin to calf (*Table 3*), but increased significantly at the ankle (mean diameter calf 2 834 ± 0·731 mm, ankle 3·040 ± 0 756 mm; *t* test $t = 2{\cdot}482$, $P < 0{\cdot}02$).

Discussion

During *in situ* saphenous vein bypass using a technique of partial vein exposure, the complexity of the saphenous vein within the unexposed thigh section is all important. Double or triple systems lying in deep and/or superficial tissue planes occur in up to 40 per cent[6,9].

Within this series the overall detection rate for complex systems was 42 per cent, much in line with our previous findings, while the 1-year bypass patency rates and revision rates remained essentially unchanged from our previous series using venography and other published series[1,4,6] These findings are even more encouraging when we reflect on the rate of back-up venography during this period. In our initial comparison of B-map and venography we felt that any double or more complex system or inadequate B-map should be backed up with either preoperative or intraoperative venography. Within this series the back-up venography rate was less than 10 per cent. This meant that at least 30 per cent of patients went to surgery with potentially complex saphenous systems without back-up venography with no apparent deleterious effect.

Assessment of vein size using B-map and venography has previously been assessed and found to be of variable accuracy[6,7,9]. Although calf vein diameter did not appear to affect the revision rate, a vein diameter of 2·5 mm seems critical in determining the feasibility of bypass. We have attempted to select the most suitable vein based on vein size at the calf, vein continuity and patency on B-map. Patients in the suitable vein group had a higher incidence of successful bypass surgery with a vein utilization rate of 97·8 per cent. A small group of patients were selected ($n = 26$) where the vein was deemed questionable. Of these, 19 underwent successfully *in situ* bypass who, on previous criteria, would have been rejected. A further three patients underwent a composite vein bypass. A final group of 25 patients had unsuitable veins; 80 per cent of these patients underwent composite vein bypass, arterial patching, or short saphenous *in situ* bypass as previously described[12]

Taylor *et al.*[2] have used the composite vein bypass as an addition to their surgical armamentarium to maintain high vein utilization rates in their reverse vein bypass series with excellent results. Despite the ability of B-map to select more favourable saphenous veins, it is not sufficiently good to allow exclusion of patients from surgery on the basis of an inadequate vein on B-map This is further emphasized by the high success rate for composite vein bypass within ours and other series[3]. One other contributing factor to the high operability and limb salvage rate in this group of patients may have been the wider application of B-map to look at the short saphenous and other superficial venous systems in an attempt to search for suitable 'bypass material'.

A more detailed assessment of vein size within the lower leg has raised an important point. that of the larger vein size at the ankle than at the mid calf level. This could be particularly important when deciding on the level of distal anastomoses. For example, if an equally good artery existed at the two sites for anastamosis, then the more distal site around the ankle, as opposed to the mid calf, might be advantageous. It is interesting that distal anastomotic vein size has been shown to correlate with bypass patency in some series[13] However, in these series no mention was made of the incidence of narrower calibre veins 'upstream' from the distal anastomosis.

There may be a further potential advantage of the larger vein size at the ankle and the ability to detect it for surgeons who perform reversed vein bypasses; namely, it has been said that one of the limiting factors to the performance of reverse vein bypass is the size of the vein to be used for the proximal anastomosis with a figure of 4 mm being suggested as the lower limit[4]. Utilizing B-map it should now be possible to select the section of vein for reversal so that optimal vein diameters exist at both extremities

From this study we have shown that B-map has allowed maintenance of equally high levels of bypass success with no increase in the bypass revision or failure rate. It must be concluded that this technique is a sufficiently good determinant of complexity of the saphenous vein to allow the maintenance of standards for arterialized *in situ* bypass surgery using a technique of partial exposure.

Finally, B-map has allowed us to look for veins from any of the superficial venous systems for their suitability as bypass conduits. In conclusion, where available, B-map should be the first line of investigation of choice to image and map the superficial veins before vein bypass surgery.

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Crossover femoral grafting to allow subsequent donor limb angioplasty

A. R. Baker and W. W. Barrie

Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK
Correspondence to: Mr W. W. Barrie

The femorofemoral crossover graft, in its present form in which a relatively short prosthetic graft is routed subcutaneously between the two common femoral arteries, was proposed by Vetto in 1962[1]. This procedure rapidly gained popularity in the treatment of high-risk patients with peripheral ischaemia due to unilateral iliac occlusive disease. Mortality and morbidity rates were low and long-term patency rates were good. As a result the indications have been broadened[2] and it has been recommended as the procedure of choice for all patients with unilateral iliac disease[3,4] In some series, up to half the patients with proximal disease coming to surgery have been treated successfully by crossover grafting[5].

Atheroma is, however, a generalized disease and aortoiliac lesions are often symmetrical[6]. With wider indications for the femorofemoral crossover graft, it is increasingly important to ensure the adequacy of the donor limb. This may be achieved by noninvasive studies[7,8], although our preference is for intra-arterial pressure measurement with papaverine testing[9]. If haemodynamically significant donor limb disease is revealed it may be treated by transluminal angioplasty at the time of operation[10,11].

With proper case selection, although there may be a deterioration of donor limb haemodynamics following operation, this should not manifest itself clinically[8,12]. Graft failure usually results from progression of recipient limb distal disease, however in 2·5–4 per cent of femorofemoral crossover grafts it follows progression in donor limb proximal disease. As the indications broaden to include patients with greater life expectancy, this is likely to become a more common problem. Failure of the standard common femoral to common femoral crossover graft necessitates further surgery, either by aortofemoral grafting with its increased mortality and morbidity rates or by axillofemoral grafting which is associated with reduced long-term patency. Progression of donor limb atheroma is very difficult to treat by percutaneous transluminal angioplasty as both groins are scarred and both common femoral arteries are sites of graft anastomoses.

We have recently been using the external iliac as the donor artery for the crossover graft (*Figure 1*). Exposure is retroperitoneal, through a very short incision placed a little above the inguinal canal The graft is tunnelled retroperitoneally along the upper border of the pubis and brought under the opposite inguinal ligament The anastomosis to the recipient artery may then incorporate a profundaplasty. We recommend this method as the donor limb common femoral artery remains intact and can be used as a route for subsequent angioplasty if disease develops in this aortoiliac segment. The undisturbed common femoral artery may also be used more easily for subsequent femoropopliteal bypass

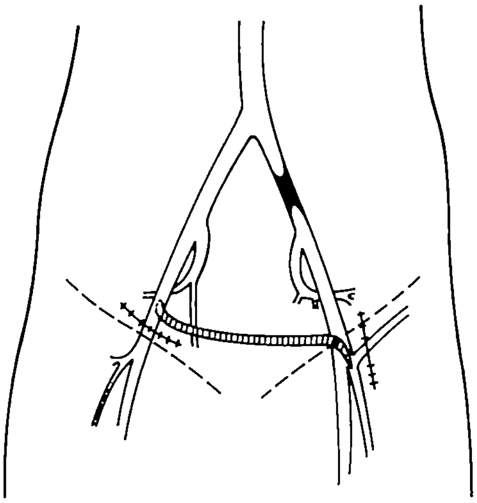

Figure 1 *Diagram of the femoral crossover graft using the contralateral external iliac artery as donor*

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Major amputation in a defined population: incidence, mortality and results of treatment

Medical records of all patients, from a defined population of 88 000 inhabitants, who underwent major lower limb amputation during 1980–82 were retrospectively scrutinized. The records showed 131 amputations were performed in 106 patients at the district hospital and 22 amputations on 17 patients at the local university hospital, referral centre, altogether 57 men and 66 women. This gave an amputation incidence of 46 per 10^5 inhabitants per year. Of the amputees 47 per cent were older than 80 years. Only two patients underwent reconstructive vascular surgery (at the university hospital) before surgery. Final amputation level was above-knee in 61 per cent of the patients treated at the district hospital. Mortality rates at 30 days and 2 years after the amputation were 23 and 56 per cent, respectively, and the age-corrected survival after 2 years was 55 per cent. For patients who came from and eventually returned to their own homes the mean hospital stay amounted to 184 days (postoperative deaths excluded). After amputation 26 patients were trained to wear a prosthesis and 16 of these used the prosthesis 2 years after amputation. The present study underlines the need for prospective and parallel studies of vascular surgery and amputation as well as analyses of the risk factors involved in lower limb ischaemia in defined populations.

Keywords: Lower limb ischaemia, amputation incidence, epidemiology

A. Kald, R. Carlsson* and E. Nilsson

Department of Surgery and
**Department of Geriatric and Long Term Medicine, Motala Hospital, S-59185 Motala, Sweden*

Correspondence to. Dr E. Nilsson

The aim of the present report is to analyse the incidence and postoperative mortality of amputation together with the hospital stay and rehabilitation of amputees treated at a district hospital (Motala Hospital) which had neither a specialized vascular surgery service nor an orthopaedic surgery service available during the study period.

Patients and methods

The medical records until the end of 1985 of all patients from the catchment area of Motala Hospital who had had major lower limb amputations at Motala Hospital or its referral centre, the University Hospital of Linkoping, between 1980 and 1982 were reviewed Below-knee amputation was performed with a long posterior musculocutaneous flap and the wound was covered by a plaster of Paris dressing postoperatively After amputation and appropriate aftercare the patients were transferred from the surgical department to the department of Geriatric and Long Term Medicine at Motala Hospital for rehabilitation in collaboration with the orthopaedic unit at the University Hospital of Linkoping

Figures used to calculate the incidence of amputation for the catchment area of Motala Hospital (88 000 inhabitants) included patients from that area amputated at the University Hospital of Linköping, whereas all other data are based only on patients treated at the Motala Hospital Age-corrected survival was calculated according to the life table method

Results

Patients and amputation incidence

From 1 January 1980 to 31 December 1982, 106 patients, 48 men and 58 women, underwent 131 lower limb amputations at Motala Hospital. The mean age of the patients was 79 years (range 28–95 years). For diabetics the corresponding figures were 76 years (28–95 years) and for patients without diabetes 80 years (61–94 years). During the same time 22 lower limb amputations (13 below-knee and nine above-knee) were performed at the University Hospital of Linköping on 17 patients from the catchment area of Motala Hospital. The mean age of these 17 patients was 72 years (range 35–90 years) The incidence of amputation in the area was thus 46 per 100 000 inhabitants per year. The numbers of amputees and inhabitants in each age decade are given in *Table 1*. In these calculations two patients amputated because of trauma were excluded.

Table 2 illustrates the disease states of patients treated at the surgical clinic in Motala for lower limb ischaemia at the time of the study. As regards those patients with diabetes, three were

Table 1 *Number of inhabitants, amputations and amputation incidence*

Age	Inhabitants	Amputees	Incidence, per 100 000/year
0–59	66 871	3	1
60–69	10 073	12	40
70–79	7 634	50	218
80–89	2 788	45	538
90–	317	11	1157
Total	87 683	121	46

Table 2 *Diseases of amputees*

Disease	Patients ($n = 106$)
Diabetes mellitus	48
Cardiac infarction, angina pectoris, congestive heart failure	67
Atrial fibrillation	15
Cerebrovascular diseases	26
Lower limb ischaemia in the contralateral extremity	19
Previous amputation in the contralateral extremity	9

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Table 3 *Diagnosis and duration of illness resulting in amputation*

	Amputations (*n* = 131)
Acute illness	16
Gangrene, developing within days	3
Atherosclerotic disease progressing within months or years	97
Unhealed previous amputation	13
Trauma	2

Table 4 *Mode of living and mortality of patients amputated in Motala hospital in the 3 years 1980–82*

Where patients lived (*n* = 106)	Before operation	After operation	
		6 months	2 years
Own home	43	26	25
Institution	63	39	22
Dead	—	41	59
Total	106	106	106

prescribed diet only, 18 had oral therapy and 27 were on insulin. Nineteen patients had bilateral lower limb ischaema, and nine had already undergone amputation of one leg. The duration of symptoms due to the disease resulting in amputation is shown in *Table 3*. In 16 cases symptoms ultimately leading to amputation started abruptly whereas three patients had had a few days illness before amputation. In 97 patients, half of whom were diabetics, amputation was preceded by a slowly progressing arterial insufficiency.

Forty-three patients (41 per cent) lived at home before being admitted with lower limb ischaemia and 63 (59 per cent) came from hospital wards or from institutions outside the hospital (*Table 4*).

Preoperative investigations

Angiography was performed on two patients. In nine cases Doppler measurements were made preoperatively, though no records of ankle pressures were found in the notes. For all other patients the indication for amputation was based on clinical examination alone.

Vascular surgery

Reconstructive vascular surgery was not performed on any of the patients who underwent amputation in Motala Hospital. During the period studied 20 patients underwent 23 embolectomies and eight of these patients (40 per cent) were amputated. Of the 17 amputees treated at the University Hospital of Linköping two had undergone reconstructive vascular surgery and one an embolectomy before amputation.

Level of amputation

Of 131 amputations 76 (58 per cent) were performed above the knee and 55 (42 per cent) below the knee. Delayed stump healing occurred in 21 patients (38 per cent) with below-knee amputation and in six patients (8 per cent) with above-knee amputation, necessitating reamputation in eight patients (15 per cent) and four patients (5 per cent) respectively, see *Table 5*.

Hospital stay

The mean stay at the surgical clinic for patients treated in Motala, postoperative deaths excluded, was 15 days For patients who came from and eventually returned to their own home the stay at the surgical clinic was 24 days and at the Department of Long Term Medicine 160 days

Mortality and rehabilitation

Mortality rate within 30 days of amputation was 23 per cent, with the highest rate (29 per cent) occurring among above-knee amputees. Of all patients, 39 per cent and 56 per cent were dead within 6 months and 2 years of amputation, respectively. For those patients who, before surgery, lived at home the corresponding figures were 37 per cent and 44 per cent The age-corrected survival figure after 2 years was 55 per cent Six months after surgery 60 per cent of patients who had initially lived at home had returned home. The mode of living and number of deaths in all patients are shown as functions of time after amputation in *Table 4*.

Of the 106 patients 26 (25 per cent) received a prosthesis, four above-knee amputees and 22 below-knee amputees. Of 43 patients who came from their own homes 19 (44 per cent) were supplied with a prosthesis compared with seven out of 63 (11 per cent) other patients Two years after amputation 16 of the 26 patients (62 per cent) trained to wear a prosthesis continued to use it in daily life.

Discussion

Amputation in populations of increasing age

Previous Swedish studies have demonstrated an increasing incidence of amputation since the beginning of this century[1–3], and the same tendency seems to prevail in the UK[4]. A population-based Danish study, however, showed a stable incidence during the 1960s[5]. Over the past 10 years amputation rates for the three largest cities of Sweden have been published; these varied from 21 to 40 amputations per 100 000 inhabitants per year[3,6,7]. In one previous study[3] 38 per cent of all amputations occurred among the 3 per cent of inhabitants who were older than 80 years compared with 46 per cent in the present report. It is appropriate, therefore, to consider the age shift which has taken place in the Swedish population over the past few decades. Within a very small overall increase in population (from 7 5 to 8·3 million) the proportion of people older than 80 years increased from 1 9 per cent in 1960 to 3·2 per cent in 1980. A similar trend, although more pronounced, took place in the defined population of the present study. Thus, in 1960 there were 1100 inhabitants older than 80 years and, in 1980 this figure was 3105—almost a threefold increase. It is, therefore, not surprising that the mean age of our patients is higher than in any previous Swedish report on amputees. Liedberg[3] found, however, that such an age shift within the population explained only part of the increase in amputations, and the same conclusion was reached in a study from the Oxford (UK) area[4]

From the present retrospective analysis no quantitative conclusion can be made concerning the most important risk factor for lower limb ischaemia—smoking habits The percentage of medically treated diabetics (45 per cent) among our patients is of the same order as in previous studies[3,7]. Only two of the 123 patients from the defined population studied had undergone reconstructive vascular surgery (in Linkoping) This is a lower figure than usually reported among amputees[3,4,8] and certainly suggests underusage of vascular surgery. (Recently, both vascular surgery and orthopaedic surgery have been introduced at our hospital.)

In contrast to previous reports, the amputation level among our patients was mostly proximal with only 39 per cent finally having below-knee amputations. Differences in amputation

Table 5 *Amputation level and complications in 131 amputations*

	Initial	Reamputation	Final level	Mortality*
Below-knee	55/119 (46)	8	47/119 (39)	8/55 (15)
Above-knee	64/119 (54)	4	72/119 (61)	22/76 (29)
Total		12		30/131 (23)

There were 119 primary amputations and 12 reamputations Values in parentheses are percentages *Within 30 days postoperatively level between defined populations may be due to differences in both treatment and age composition of the populations. Below-knee amputation in more than 70 per cent of amputees has been seen in some recent studies[3,8] The importance of orthopaedic knowledge covering both amputation surgery and rehabilitation is emphasized in several recent reports[3,6,7]. Relatively few (25 per cent) of our patients were trained to walk with a prosthesis[9], but 62 per cent of these amputees continued to use their prosthesis 2 years later.

In the present study, hospital stay at the surgical clinic was short (15 days). On the other hand, a long time was spent at the Department of Geriatric and Long Term Medicine. Even for those patients who came from, and eventually returned to, their own homes it amounted to 160 days. The age-corrected survival of our patients 2 years after amputation was 55 per cent which is in accordance with previous data from unselected populations[1,5,10]. Hansson[1] concluded that the mortality rate following amputation was four times greater than expected.

Preventive measures and the need for prospective studies

It has been indicated that treatment of diabetes and heart disorders are of great importance in lowering the incidence of amputation[10] Preventive medicine in this field should also include improvement of the patients' smoking habits, and early treatment of dysvascular foot lesions[11].

Vascular surgery is rapidly expanding in Scandinavia[12] but its role in prevention of major amputation is far from settled. There is a great need for prospective and parallel studies of both vascular and amputation surgery in defined populations. In such reports the number of vascular procedures and amputations as well as crude and age-corrected survival figures are necessary to allow meaningful comparisons. It should also be pointed out that in many respects limb salvage is a better end point than graft patency in the evaluation of vascular surgery[13].

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Short note

Br. J. Surg. 1989, Vol. 76, March,
311–312

Effect of shoulder immobilization on wound seroma and shoulder dysfunction following modified radical mastectomy: a randomized prospective clinical trial

I. Dawson, L. Stam, J. M. Heslinga and H. L. Kalsbeek

Department of Surgery, Bronovo Hospital, PO Box 96900, 2509 JH The Hague, The Netherlands
Correspondence to: Mr I Dawson

Wound seroma and shoulder dysfunction are the most frequent complications of a mastectomy[1,2]. To prevent the development of a frozen shoulder it seems justifiable to recommend postoperative exercises. However, early shoulder exercises may have a deleterious effect on wound healing and seroma formation.

The purpose of this study was to determine the effect of temporary shoulder immobilization on wound seroma and shoulder dysfunction following modified radical mastectomy.

Patients and methods

From March 1984 to October 1986, 100 women who underwent a modified radical mastectomy were randomized into two groups. The exercise group ($n = 51$) started to exercise on the first postoperative day. In the immobilized group ($n = 49$) the ipsilateral arm was immobilized in a sling for 5 days; then the same shoulder exercises were started. The two groups were comparable (*Table 1*).

On the fifth postoperative day, the suction drain (Redon* 14 Fr) was removed and the drainage volume recorded. Subsequently the wound was inspected daily. In the event of a seroma, aspiration followed until resolution.

To assess shoulder function, abduction and anteflexion were measured. All measurements were performed by the same individual. The corrected χ^2 test and Student's two-tailed t test were used for statistical analysis.

Table 1 *Comparison of related factors for the two trial groups*

Characteristics	Exercise group ($n = 51$)	Immobilized group ($n = 49$)
Physical factors		
Age (years)	64 ± 12	65 ± 14
Quetelet index (kg/m)^2	24 ± 4	24 ± 5
Shoulder function:		
Anteflexion (°)	154 ± 10	152 ± 10
Abduction (°)	152 ± 10	149 ± 11
Technical factors		
Staff surgeon: resident	26:25	24:25
Length of operation (min)	75 ± 15	73 ± 17
Tumour factors		
Tumour size (mm)	24 ± 13	25 ± 15
Involved lymph nodes (n)	2 ± 3	2 ± 4
Adjuvant irradiation*	24 (47)	21 (43)

Values are mean ± s.d. except where indicated (*). Percentages are given in parentheses

Results

The drainage volume for the exercise group was 15 per cent more than that for the immobilized group (379 *versus* 322 ml, *Table 2*). This difference approached statistical significance. Seromas developed more often in the exercise group but no significant difference was found in volume, duration or number of aspirations.

Four patients (8 per cent) from the exercise group and one (2 per cent) from the immobilized group exhibited delayed wound healing. Infections were seen only in the exercise group. In both groups there was one haemorrhage which required intervention.

Table 3 shows the limitation of shoulder function at discharge. A mean decrease in anteflexion of 7° and in abduction of 10° was noted for the exercise group, compared with about 10° for both functions in the immobilized group. These differences were not significant. The number of patients with a functional loss of more than 15° was slightly higher in the immobilized group.

Discussion

As the characteristics of the mastectomy wound predispose to seroma formation and shoulder dysfunction, every effort should be made to minimize these problems. Since the era of the Halsted radical mastectomy, much emphasis has been placed on the prevention of a frozen shoulder[2,3], but only a few studies have evaluated the risks and benefits of these exercises.

In two randomized prospective studies[4,5], shoulder immobilization for 7 days reduced the drainage volume significantly. However, after radical mastectomy this resulted in unacceptable shoulder dysfunction lasting 4 months[4]. In the

Table 2 *Total drainage volume, management of wound seromas and incidence of wound complications*

	Exercise group ($n = 51$)	Immobilized group ($n = 49$)
Drainage volume* (ml)	379 ± 208	322 ± 169
Wound seroma†	30 (59)	21 (43)
Volume* (ml)	427 ± 468	460 ± 504
Duration* (days)	17 ± 11	15 ± 8
Aspiration* (n)	4 ± 3	5 ± 4
Delayed wound healing‡	4 (8)	1 (2)
Infection§	3 (6)	0 (0)
Haemorrhage	1 (2)	1 (2)

* Values are mean ± s.d. Percentages are given in parentheses; † defined as > 10 ml serous fluid collection, thus requiring aspiration; ‡ defined as separation of wound edges or late removal of sutures (> 12 days); § defined as requiring either antibiotics or open drainage

Table 3 *Limitation of shoulder function at discharge from hospital*

	Exercise group ($n = 51$)	Immobilized group ($n = 49$)
Mean limitation		
Anteflexion* (°)	7 ± 9	10 ± 9
Abduction* (°)	10 ± 11	11 ± 10
Limitation > 15°		
Anteflexion†	7 (14)	11 (22)
Abduction†	11 (22)	14 (29)
Postoperative stay* (days)	14 ± 3	15 ± 4

* Values are mean ± s.d. † Number of patients with percentages in parentheses

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other study[5], no significant difference in shoulder function was noted when the exercise and immobilized group were compared 1 month after axillary dissection for melanoma or breast cancer.

In our study of modified radical mastectomy patients the period of immobilization was set at 5 days. As a result, preoperative shoulder function was achieved sooner than in the above-mentioned studies. Fourteen days after surgery no significant difference in function was observed.

In addition, there was a trend towards decreased drainage volume and a lower incidence of seroma formation in the immobilized group, which may represent an advantage of delayed shoulder exercises and merit continued study. As no adverse effect on shoulder function has been shown, routine shoulder exercises before the fifth postoperative day should be abandoned.

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Surgical workshop

Br. J. Surg. 1989, Vol. 76, March, 312

A simple specimen mount for the orientation of breast biopsies

P. G. Bentley

The Nuffield Hospital, Tunbridge Wells, Kent, UK

As a result of the wider use of screening mammography, surgeons are increasingly called on to excise impalpable lesions. Such specimens require postexcisional radiographs to confirm removal of the lesion and to guide the pathologist to the abnormal area, which may not be exactly at the tip of the localizing guide wire. Correct orientation of the specimen is essential and this paper describes a simple and inexpensive aid.

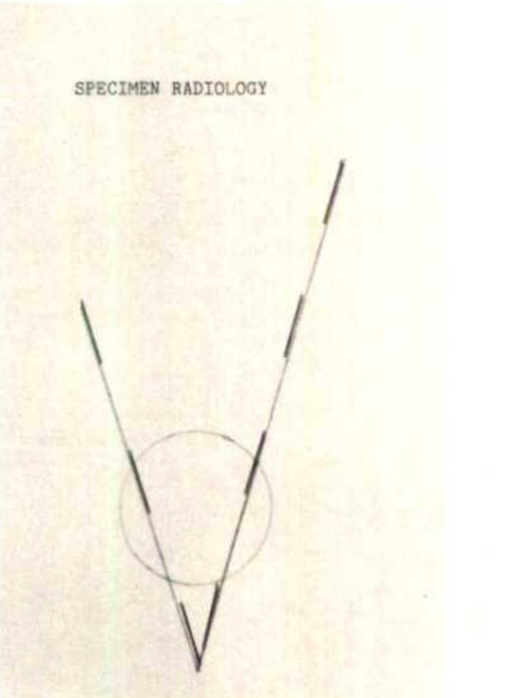

Figure 1 *White fibre-free card marked with staples in the form of a* V

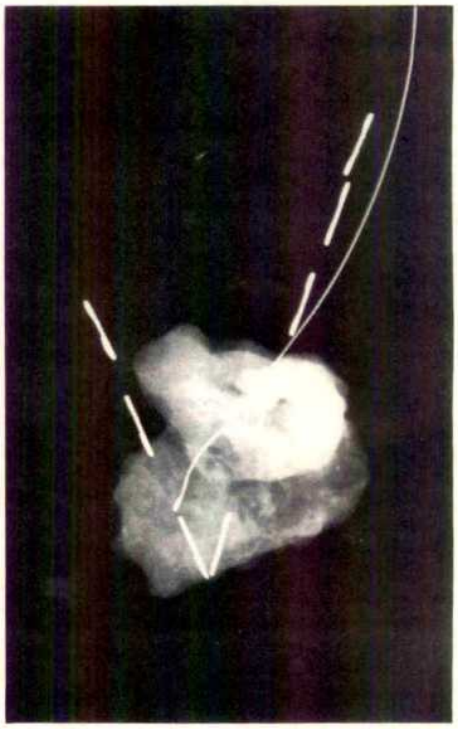

Figure 2 *The card and specimen are X-rayed to confirm that the abnormal area has been included*

A piece of white, fibre-free card is marked with staples in the form of a V with limbs of unequal length (*Figure 1*). The card and staples are then autoclaved and packed separately ready for use. Following hook-wire localization and surgical removal of the area of breast tissue, the specimen is placed on a card and sewn to it with a silk stitch at three sites around the periphery. The card and specimen are then X-rayed to confirm that the abnormal area has been included (*Figure 2*) and then the whole card and specimen are immersed in formalin and sent to the pathologist. The position of the lesion can then be found easily and multiple blocks taken of this area. The difference in length of the arms of the V ensures that the X-ray is not reversed.

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Biliopancreatic bypass in the Prader–Willi syndrome

J.-J. Brossy

Department of Surgery, Victoria Hospital, Cape Town, South Africa

Correspondence to: Mr J.-J. Brossy, Department of Anatomy and Cell Biology, University of Cape Town Medical School, Observatory, 7925 Cape Town, South Africa

The Prader–Willi syndrome (PWS) is an uncommon childhood condition probably due to an abnormality of chromosome 15 (References 1 and 2). It presents as mental retardation, hypotonia, hypogonadism and obesity. Hyperphagia starts at the age of 2–3 years and within a decade the victims are grossly obese. The mental state makes dieting difficult and food theft is common. This provokes severe friction in the family.

Case report

A 31-year-old man showed the classic features of PWS. He was the eldest of three children; the two siblings were female and normal. His mental development was adequate to allow conversation but his comprehension was questionable. He goes to sheltered employment. His height is 163 cm and when first seen he weighed over 100 kg and became dyspnoeic on walking 50 m on level ground. His thighs and calves were huge and he had pitting oedema. He could eat anything which was offered him and never felt full. He was co-operative when the problem was discussed but in practice was unable to control the hyperphagia. The need to ration his food led to a highly emotional stress and he deeply resented his parents' attempts to control his intake.

On considering surgical management it was clear that gastric stapling would, if anything, aggravate the emotional issues so a biliopancreatic bypass[3] was proposed (*Figure 1*). This is a major operation and morbidity in obese patients includes infection, pulmonary complications and incisional hernia. Diarrhoea is seldom severe and nutritional deficiencies are uncommon. Except for the excised part of the stomach, the operation is reversible, although this is rarely needed.

The operation was discussed in detail with the patient and family. His blood biochemistry was carefully checked and he was prepared with a routine of exercises. The surgery was uneventful and at its termination the patient was able to breathe spontaneously so he was extubated. He was nursed in a sitting position, in a chair; a bed was avoided, even at night. In this position respiration is unhindered and assisted ambulation is much easier. Our patient did well, was home within a week and back at work in the third week.

Discussion

It is now established that hunger and satiety are both under the control of centres in the hypothalamus[4]. Owing to defects in one or both centres the PWS patient experiences no feeling of fullness. Dietary discipline takes enormous effort and is impossible to maintain. Soper *et al.*[5] performed gastric stapling in about 40 children including 7 with PWS but the results were disappointing: the very small capacity leads to overeating with nausea, vomiting, oesophagitis and peptic ulcer. A previous report of a jejunoileal shunt[6] with a successful outcome encouraged us to consider this option for our patient. Three years later he has lost 20 kg, can walk considerable distances, and eats more or less what he wants. His bowels work 2–4 times a day but he has good control. His blood parameters remain normal. He feels well and the tension and friction at home have disappeared. We believe that this operation should be considered in all PWS patients who survive to their teens.

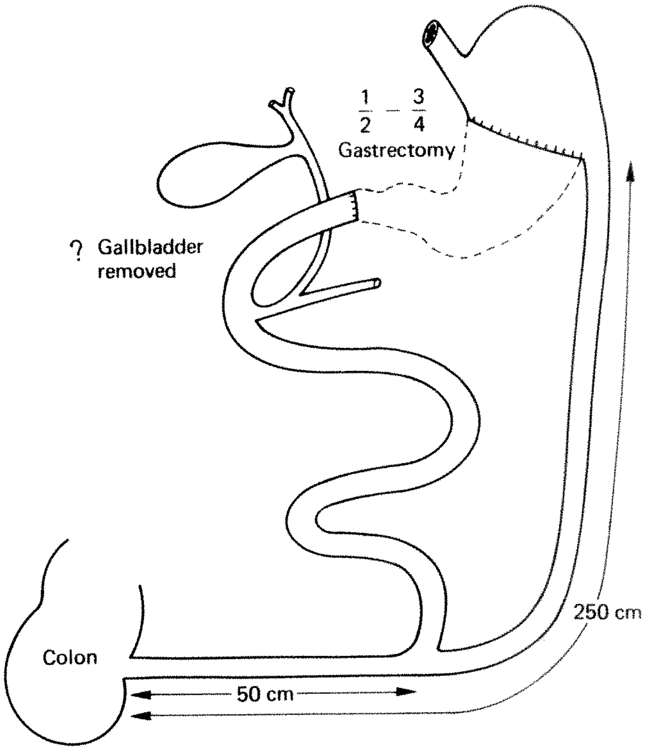

Figure 1 *Biliopancreatic bypass, after Scopinaro et al.*[3]*. The operation involves resecting about half of the stomach and closing the duodenum. The small intestine is then divided about two-thirds of the way down; the lower, ileal loop is taken up to the gastric remnant and the upper, jejunal loop is anastomosed to the lower loop 50 cm from the caecum, which thus becomes the only part of the gut where mixing of food with digestive juices and absorption can take place. It is effectively a very long Roux-en-Y loop*

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Peritoneal lavage with mercuric chloride: toxic and unnecessary

J. S. Friedland and P. J. T. Vallance

Renal Unit, Guy's Hospital, St. Thomas Street, London SE1, UK

Correspondence to: Dr P. J. T. Vallance, Department of Pharmacology and Clinical Pharmacology, St. George's Hospital Medical School, London SW17 0RE, UK

Mercuric chloride is the most toxic of the inorganic mercury salts and can cause tissue corrosion, neurotoxicity, acute renal failure and circulatory collapse[1]. Mercuric chloride solutions are still used as topical anticancer agents in operations for colorectal carcinoma despite the known risk of precipitating acute renal failure and even death[2]. We report on a patient who developed severe mercury toxicity and who subsequently died following intraperitoneal instillation of mercuric chloride solution.

Case report

A previously fit 70-year-old man underwent uncomplicated right hemicolectomy for a Dukes' C adenocarcinoma. Within 24 h of surgery the patient had become severely unwell and anuric. Shortly afterwards he was transferred to the Intensive Therapy Unit at Guy's Hospital under the care of the Renal Unit. On examination he was confused, drowsy, dehydrated and had a coarse tremor of both hands. The pulse rate was 100 beats per min and blood pressure was 100/60 mmHg with a central venous pressure of $+3\,\mathrm{cmH_2O}$. On examination of the chest there was a right-sided pleural effusion. The abdomen was tender with widespread guarding and rebound tenderness maximal in the right lower quadrant. Serum urea and serum creatinine were raised at 17·6 mmol litre^{-1} (normal range 2·5–7·5 mmol litre^{-1}) and 590 μmol litre^{-1} (normal range 50–130 μmol litre^{-1}) respectively.

An intravenous infusion of colloid increased the central venous pressure to $+9\,\mathrm{cmH_2O}$, and the blood pressure to 150/65 mmHg. A dopamine infusion was started at 2·5 μg kg^{-1} min^{-1} and urine flow rates of over 100 ml h^{-1} were achieved. After extensive microbiological sampling, all of which was later found to be negative, broad-spectrum antibiotic therapy was instituted. The patient remained unwell requiring ventilation and intravenous feeding. In view of worsening abdominal signs he underwent repeat laparotomy. The anastomosis was found to be intact. However, there was marked erosion of the posterior abdominal wall with bloody, purulent fluid in the right paramedian, subhepatic and pelvic spaces.

Postoperatively the patient remained unwell with severe abdominal tenderness. At this stage, it was reported by the referring hospital that, before closure of the original wound, 50 ml of 1:500 mercuric chloride solution was instilled intraperitoneally. Forty-eight hours after the initial operation the blood mercury level was found to be 560 μg litre^{-1} (toxic range >50 μg litre^{-1}) and the urine level was 2700 μg litre^{-1}. Treatment was started with intravenous 2,3-dimercapto-1-propanesulphonate, a chelating agent which has been widely used in the USSR, and which is being evaluated for the treatment of mercury toxicity by the Poisons Unit at New Cross Hospital, London, UK. High levels of mercury clearance were achieved as renal function improved, with the serum creatinine falling to 293 μmol litre^{-1}. The patient was weaned from the ventilator and neurological function showed signs of improvement. However respiratory problems with recurrent large pleural effusions persisted and 8 days after admission the patient became asystolic. Attempts at resuscitation were unsuccessful. Post mortem revealed high levels of mercury in the liver (5950 μg kg^{-1}), the renal cortex (8800 μg kg^{-1}) and the renal medulla (7499 μg kg^{-1}).

Discussion

The clinical manifestations of acute inorganic mercury toxicity have been well described[1,2,4]. This patient developed severe local and systemic manifestations of mercury toxicity within 24 h of the intraperitoneal instillation of 50 ml of 1:500 mercuric chloride solution, and subsequently died following the development of pulmonary complications. The use of mercuric chloride solutions for peritoneal lavage was first reported to cause acute renal failure more than 20 years ago[2]. Subsequent reports of serious adverse effects, including five known deaths associated with its use, were reviewed as recently as 1984[2]. The efficacy of mercuric chloride as a local cancericidal agent has been questioned[2,5] and, while local irrigation of the bowel with 1:500 mercuric chloride solution may not be associated with toxicity, the practice of using the solution or similar ones for peritoneal lavage can no longer be justified and should now cease.

Acknowledgements

We should like to thank the Poisons Unit, New Cross Hospital, London, UK for providing mercury levels.

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Pathology of Neck Injury

Peter Vanezis, MD, MRCPath, DMJ(Path)
Senior Lecturer in Forensic Medicine, Department of Forensic Medicine, The London Hospital Medical School, UK.

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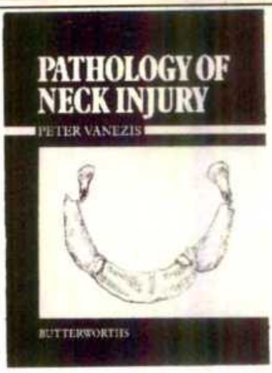

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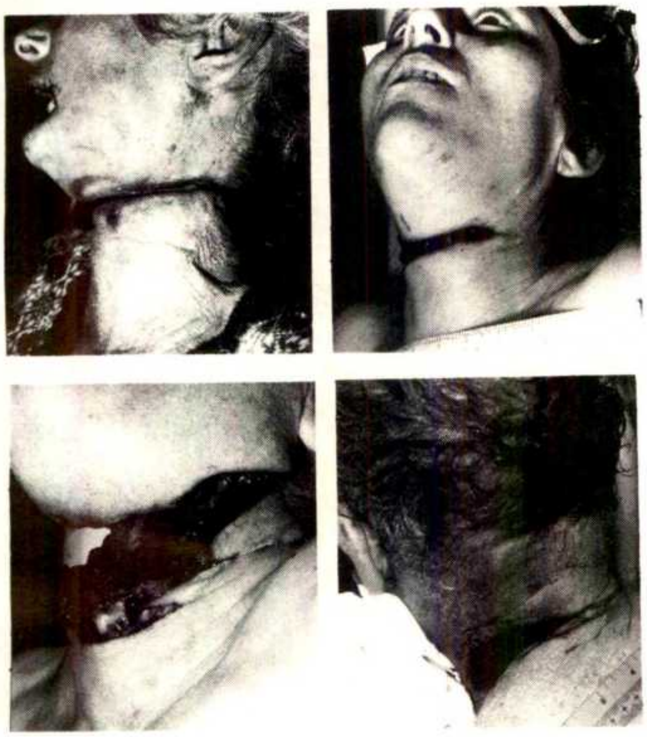

Where appropriate, and especially with regard to penetrating and compressive modes of trauma, the interpretation of injuries and their differentiation into various categories such as homicidal, accidental or suicidal has been emphasized.

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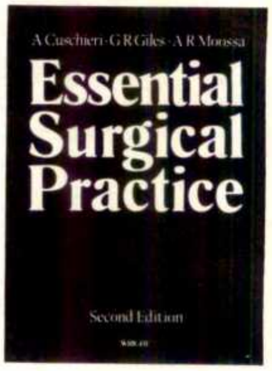
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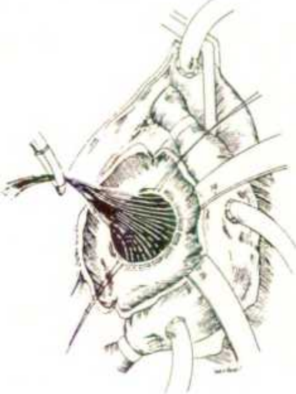

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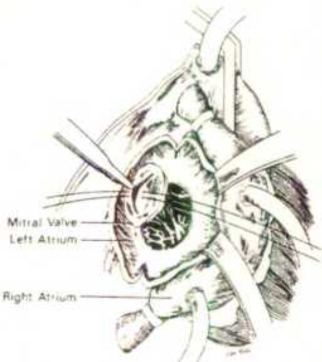

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Correspondence

Wound infection after appendicectomy

Sir

I read with great interest the review of wound infection after appendicectomy by Krukowski and colleagues (*Br J Surg* 1988; **75**: 1023–33).

The authors assume that the degree of operative contamination of the wound is one of the most important determinants of infection.

However, they state that 'quantitative bacteriology is laborious and has not been attempted in any clinical studies of wound infection after appendicectomy'.

This has been done recently in a study of 65 patients with perforated appendicitis[1]. During operation, the wound (and appendix) was sampled using velvet pads which were transported in an anaerobic atmosphere, shaken and rinsed, and cultured in an anaerobic cabinet.

In 15 patients who became infected, significantly higher densities of both aerobic and anaerobic bacteria were measured on the appendical surface and in the wound than in 50 patients who remained uninfected.

The median infective dose of bacteria (predominantly *Escherchia coli* and *Bacillus fragilis*) was $4{\cdot}6 \times 10^5$ c.f.u./cm^2 wound.

The study also demonstrated a high correlation between the density of wound bacteria and postoperative wound infection.

D. Raahave

University of Copenhagen
Anemonevej 24
Denmark

1. Raahave D, Friis-Møller A, Bjerre-Jepsen B, Thiis-Knudsen J, Rasmussen LB. The infective dose of aerobic and anaerobic bacteria in postoperative wound sepsis. *Arch Surg* 1986; **121**: 924–9.

Author's reply

Sir

We regret having overlooked the important paper by Dr Raahave and his colleagues. They have clearly demonstrated the impact of operative contamination on the frequency of postoperative wound infection after appendicectomy.

We are concerned that a relevant paper should have escaped our notice and have reviewed again the 1986 and 1987 issues of *Index Medicus*. The paper is cited in the 1986 Author Index but does not appear in the 1986 or 1987 Subject Indices under any of the categories relating to the Appendix, although we have found it, in retrospect, under 'Bacteria, anaerobic/isolation and purification' and 'Surgical wound infection/microbiology'. Unfortunately the title did not alert us to its relevance to perforated appendicitis.

Z. H. Krukowski
N. A. Matheson

Aberdeen Royal Infirmary
Aberdeen AB9 2ZB
UK

Wound instillation for postoperative pain relief

Sir

It is with great interest that we read the recent article by Gibbs *et al.* (*Br J Surg* 1988; **75**: 923–4) which did not demonstrate any difference between bupivacaine and saline in wound perfusion after cholecystectomy. Their results mirror those of our recently completed study.

Seventy patients having elective aortic surgery were randomized to receive either 40 ml 0·25 per cent bupivacaine or saline every 4 h for a total of 48 h into indwelling wound irrigation catheters. In transverse incisions two catheters were randomly placed either in the rectus sheath or subcutaneously; in vertical incisions one catheter was placed subcutaneously.

There was no significant difference in either pain scores, morphine requirements or parameters of pulmonary function between the saline ($n = 33$) and the bupivacaine ($n = 37$) groups. Siting of the catheters in the transverse groups made no difference. The mean pain score on the first postoperative day was lower ($P < 0{\cdot}05$) in patients with transverse ($n = 49$) than in those with vertical ($n = 21$) incisions.

U. Pfeiffer
G. A. McLoughlin
M. E. Dodson

Royal Liverpool Hospital
Liverpool L7 8XP
UK

Benign breast lump

Sir

The article by Sainsbury *et al.* (*Br J Surg* 1988; **75**: 1080–2) on the natural history of the benign breast lump is a worthy addition to a valuable series from their unit but cannot be allowed to pass without comment. Their case rests on a 100 per cent success rate in obtaining adequate biopsies and their faith in the predictive value of a benign report. Their series contained four carcinomas diagnosed on cytology but not clinically. This is consistent with the experience of Wilkinson and Forrest[1] who had a 6 per cent incidence of carcinoma in their series of 134 clinical fibroadenomas.

In our own series of 75 clinical fibroadenomas (discrete, well demarcated, smooth, mobile, painless breast masses) with cytological and histological diagnoses, there was a 5 per cent incidence of malignancy. The authors' performance in obtaining 100 per cent adequate biopsy rate is remarkable. In our own series biopsies were inadequate for diagnosis in 16 per cent of 51 proven fibroadenomas and 54 per cent of the other lesions, including one carcinoma. Cytological diagnosis of breast cancer is highly specific but by no means 100 per cent sensitive. Although the Newcastle group's performance in confirming benign disease (where clinical diagnosis is 95 per cent accurate) is enviable, the crux of their paper is the four cancer cases. Can they tell us how many repeat biopsies were necessary in this series, and whether the repeat biopsy rate was operator-dependent? Are they certain that they can achieve 100 per cent sensitivity in the diagnosis of breast cancer in these small mobile lesions? Does a series of four cases allow them to be sure that they will never be misled by a genuine benign report from a pathologist misled by a sampling error?

It comes as no surprise to breast surgeons to know that many benign lumps will resolve spontaneously (even though some would remain sceptical about the authors' ability to convince us that they can diagnose fibroadenoma accurately without histology). Using strict clinical criteria we can all accurately diagnose benign disease in young women in whom breast cancer is rare. Perhaps we need a larger series than this, with four cases, to prove that these rare cancers will not be missed, even occasionally, if a non-excisional policy is pursued by groups less skilled in cytological biopsy and diagnosis than Mr Sainsbury and his colleagues.

M. Burke

Northwick Park Hospital
Harrow HA1 3UJ
UK

1. Wilkinson S, Forrest APM. Fibro-adenoma of the breast. *Br J Surg* 1985; **72**: 838–40.

Author's reply

Sir

Thank you for allowing me to see Mr Burke's letter and to comment. Mr Burke is right to point out that the crux of our paper is the four cancer cases. No repeat biopsies were needed to diagnose these four which were all found at their first visit to the clinic. Repeat biopsies were needed in this series in 17 per cent of cases. These were nearly all operator-dependent, having initially been carried out by the senior house officer who attends the clinic for training purposes. In these cases the repeat specimen was obtained by either the consultant or senior registrar. I think that both operator dependency and good cytopathological interpretation are vital. We are extremely fortunate in having an experienced pathologist whose initial, inclinic report is highly accurate[1]. We are quite aggressive with the needle cytology and a thorough biopsy of the area is obtained. I do not think we can ever be certain of 100 per cent sensitivity in diagnosis of breast cancer in the small mobile lesion but all four of the cancers were diagnosed at first visit.

I agree with Mr Burke's comment that a larger series is needed. I think one of the messages of our paper was that, given strict clinical and cytological criteria, not all breast lumps need excising in young women, given that an accurate cytological and clinical diagnosis has been made.

J. R. C. Sainsbury

The Royal Infirmary
Huddersfield HD3 3EA
UK

1. Nicholson S, Sainsbury JRC, Wadehra V, Needham GK, Farndon JR. Use of fine needle aspiration cytology with immediate reporting in the diagnosis of breast disease. *Br J Surg* 1988; **75**: 847–50.

Endoscopic sphincterotomy

Sir

We read with interest the paper by Messrs Lambert, Martin and Tweedle (*Br J Surg* 1988; **75**: 896–8) which describes their experience of endoscopic sphincterotomy for retained bile duct stones. They reported a success rate of 86 per cent, a complication rate of 19 per cent (or 15 per cent if occult haemorrhages are excluded), and a mortality rate of 1·3 per cent, and understandably recommended that the technique should only be used when other non-operative treatments are inappropriate or have failed. However, they failed to point out that their results differed markedly from those of all previous reports on the subject[1–4]. Four previous reports (two of which were admittedly only small series) reported success rates of 95–100 per cent, complication rates of 0–8 per cent, and no deaths occurred. The collective results for 135 patients were a success rate of 96 per cent and a complication rate of 3 per cent. We have treated 32 patients (within 14 days of operation in 14 patients) and have achieved complete duct clearance in 28 (88 per cent) with a complication rate of 3 per cent (a single patient whose haemorrhage was treated conservatively).

We feel that these results compare favourably with those of other non-operative treatments and endoscopic sphincterotomy has the advantage of allowing the retained stones to be removed during the same admission. We no longer regard the discovery of retained stones with dismay and indeed there may be instances when it is safer to leave stones behind for later endoscopic removal rather than to risk damaging the bile duct by persistent attempts at operative removal.

K. I. Bickerstaff
R. W. Chapman
B. J. Britton

John Radcliffe Hospital
Oxford OX3 9DU
UK

1. Soehendra N, Kempeneers I, Erchfuss HP, Reynders-Frederic V. Early post-operative endoscopy after biliary tract surgery. *Endoscopy* 1981; **13**: 113–17.
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4. O'Doherty DP, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for retained common bile duct stones in patients with T-tube *in situ* in the early post-operative period. *Br J Surg* 1986; **73**: 454–6.

Fine needle aspiration cytology

Sir

The conclusions of Nicholson *et al.* (*Br J Surg* 1988; **75**: 847–50) on the accuracy of fine needle aspiration cytology in breast disease appear to be unsound. Cytology was one of the determinants of excision and 'confirmatory' histology. Excision and histology were carried out only in a minority of patients with benign cytology and histology was also not available in elderly patients with malignant cytology. Surely the predictive accuracy of cytology can be reliably determined only by a blind comparison with histology; the assumption that patients without histology had benign disease (or malignant in the elderly) invalidates the analysis. If we overlook the elderly patients assumed (without histology) to have malignant disease, a false positive rate may be calculated, but none of the other predictions of the decision analysis (false negative rate, sensitivity, specificity and diagnostic accuracy) is valid since there is no histological information on which true negative and false negative cytology may be established. When the authors give figures of 96 per cent for diagnostic accuracy, 90 per cent for sensitivity and 99 per cent for specificity, they are also ignoring the high frequency of aspirates unsatisfactory for cytology (28 per cent), although this is a more minor criticism than that of the lack of histological information in the majority of their patients, which appears to invalidate their claims.

N. A. Matheson

Aberdeen Royal Infirmary
Aberdeen AB9 2ZB
UK

Author's reply

Sir

Thank you for allowing me to reply to Mr Matheson's comments about our paper 'Use of fine needle aspiration cytology with immediate reporting in the diagnosis of breast disease'.

The study did not set out to compare fine needle aspiration cytology (FNAC) with open biopsy. Its objectives were to compare the ability of FNAC to be used as a diagnostic method in the clinic, and measurements of sensitivity, specificity and accuracy were used to compare immediate reports (achieved in the clinic) with definitive reports, issued when all slides from each patient had been reviewed and a definitive cytological diagnosis achieved at a later time in the cytology laboratory. These points were emphasized: 'This study examines the feasibility and accuracy of FNAC in immediate reporting'. *Table 3* shows the comparisons between immediate and definitive cytology results and, similarly, our conclusions try to point out that 'there was no significant difference in any category between immediate and definitive reporting'.

Unsatisfactory cytology preparations were excluded from the final analysis because these were not acceptable as part of the clinical appraisal in these patients. A repeat aspirate would have been performed or other modalities would have been employed (clinical examination and follow-up with mammography) to achieve diagnosis. The main aim of using fine needle aspiration biopsy in the assessment of patients with breast disease is to limit excisional biopsy. Extended follow-up of patients in this study with cytologically proved benign breast disease has validated this action[1]. In elderly patients without 'confirmatory' excisional biopsy, very careful follow-up and assessment of response to primary endocrine therapy leaves little doubt as to the accuracy of fine needle biopsy[2].

The use of FNAC in breast disease is only slowly gaining acceptance. All studies which compare its accuracy with excisional biopsy show that this is a highly accurate technique. It has been shown to be more accurate than core needle biopsy.

We do not believe our claims go beyond the allowances of the data and analysis that we have presented.

J. R. Farndon

Bristol Royal Infirmary
Bristol BS2 8HW
UK

1. Sainsbury JRC, Nicholson S, Needham GK, Wadehra V, Farndon JR. Natural history of the benign breast lump. *Br J Surg* 1988; **75**: 1080–2.
2. Nicholson S, Halcrow P, Sainsbury JRC *et al.* Epidermal growth factor receptor (EGFr) status associated with failure of primary endocrine therapy in elderly postmenopausal patients with breast cancer. *Br J Cancer* 1988; **58**: 810–14.

Intragastric pH and duodenal ulcer

Sir

I read with interest the results of Rogers *et al.* (*Br J Surg* 1988; **75**: 961–5) concerning 24-h intragastric pH monitoring and would like to raise two points.

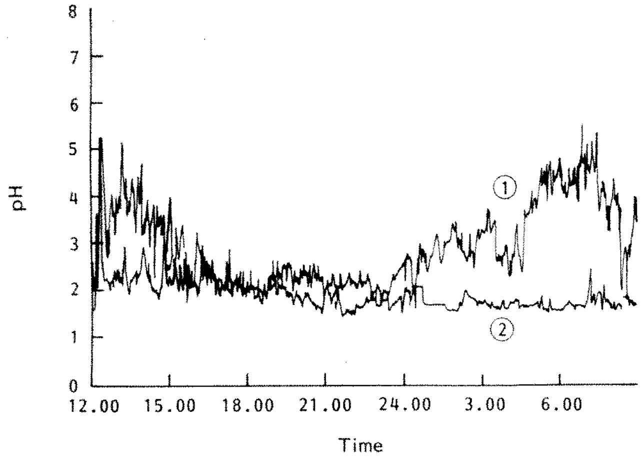

Figure 1 *Postoperative median pH curves of the group with ② and without ① ulcer recurrences, respectively*

The intraindividual day-to-day variation of 24-h intragastric pH monitoring cannot be proved by the median 24-h pH of 28 subjects on two separate occasions. Even if the values of this group were exactly the same on two separate occasions, this does not exclude the possibility that the median pH over the 24 h, or at least certain phases of it, might vary considerably on two different days in the individual[1].

The authors' conclusion from the measurements after highly selective vagotomy (HSV), suggesting a lesser importance of the suppression of nocturnal acidity for the healing of duodenal ulcers, is not based on convincing results. Rogers *et al.* have assumed that most of the 20 vagotomies (median night-time pH 1·7) had been 'complete' although three patients had a positive insulin test by Hollander's criteria and two patients had no test. Moreover, the predictive value of the insulin test is very poor due to its low sensitivity and specificity[2,3]. Before drawing such conclusions one would expect that the effect of vagotomy would be evaluated on a more reliable basis. The best criterion for evaluation of HSV is ulcer recurrence. We have compared the results of long-term intragastric pH monitoring in 42 patients without ulcer relapse and ten patients with ulcer recurrence after HSV (median time of follow-up, 3·9 years, range 2·4–6·1 years)[4,5]. The postoperative median 24-h pH of the group without recurrence was 2·7, which is similar to that in the report by Rogers *et al.*, but in patients with recurrence the pH was 1·9 (P=0·03). The most significant difference between both groups, however, could be found during the nocturnal period (from 20.00 hours to 06.00 hours): in patients with ulcer recurrence, the median pH was 1·7; for those without recurrence, the pH was 3·7 (P<0·01, *Figure 1*). Correspondingly, the most significant difference of the percentage of pH values lower than 2·0 between patients with and without recurrence, respectively, was found during the nocturnal phase (87 *versus* 20 per cent, P<0·001). A postoperative nocturnal median pH of < 2·0 was closely correlated with the occurrence of ulcer relapse. Our findings are in close accordance with the results of Gotthard *et al.* who have not been cited but who demonstrated in 1986 (with pH curves very similar to ours) that high nocturnal acidity is a predisposing factor for ulcer recurrence after HSV[6]. Hence, in accordance to Dragstedt's teaching, these facts support the view that suppression of nocturnal acidity is of crucial importance in the healing of duodenal ulcers.

A. H. Hölscher

Technical University of Munich
8000 Munich 80
FRG

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Management of pelvic space

Sir

We read with interest the recent article by S. R. G. Smith *et al.* (*Br J Surg* 1988; **75**: 1012–5) regarding the management of the pelvic space following rectal excision. We shared their concern that pelvic drains may have a detrimental effect on rectal anastomoses and possibly lead to anastomotic dehiscence. We undertook four low anterior resections without drainage. Three of the four patients had major problems with anastomotic leakage and sepsis. This dramatic experience without drains has prompted the introduction of a 2 Redivac® (Biomet Ltd., Bridgend, UK) drainage regime with one leak in 19 subsequent cases. We place particular importance on the early activation of drainage during abdominal closure to prevent the early accumulation of clot in the pelvis.

We routinely mobilize the splenic flexure and appreciating the beneficial protective value of the omentum mobilize it from the colon and introduce it anteriorly into the pelvis and allow it to drape laterally around the anastomosis. We do not mobilize the omentum from the stomach and rarely have difficulty in obtaining sufficient omentum to fill the pelvis. The omentum is tethered in the upper abdomen by its attachment to the colon and, particularly, by its attachment to the splenic flexure.

Smith *et al.* have presented a series of patients which differ in the extent of resection. Our current feeling about the group of patients undergoing low anterior resection with total mesorectal excision is that pelvic drainage is necessary.

D. J. Schache
N. D. Karanjia
R. J. Heald

Basingstoke District Hospital
Basingstoke RG24 9NA
UK

Tumour calcification after hepatic dearterialization

Sir

In response to the letter by our colleagues Messrs Charnley and Morris (*Br J Surg* 1988; **75**: 1150) we would like to add the following information. We were asked by the Editor to shorten our report, and several other reports on tumour calcifications following therapy were removed from the discussion. Calcifications in liver tumours are extremely rare. They are more common in primary liver cancer than metastatic disease[1]. In 1984 Schlanger and Wils[2] reported a patient in whom extensive tumour calcification had occurred in hepatic metastases from colonic cancer after hepatic artery infusion with 5-fluorouracil, Adriamycin® (Farmitalia Carlo Erba, St. Albans, UK) and mitomycin C. On publication this patient was alive and well after 28 months. In another study of ^{131}I antiferritin administration to patients with unresectable hepatomas, tumour calcification appeared in only those who responded to treatment[3]. The patient who survived the longest (3·5 years) without evidence of recurrent disease showed massive tumour calcifications. In the one study mentioned in our discussion, tumour calcification appeared concomitantly with a fall in carcinoembryonic antigen and a reduction of symptoms in a patient with hepatic metastases from *Pseudomyxoma peritonei* who was treated with intraperitoneal 5-fluorouracil[4].

There are thus several reports in the literature of tumour calcifications induced by different therapies appearing concomitantly with other signs of tumour regression.

In our discussion we state that the appearance of tumour calcification might be due to the combined effects of temporary dearterialization and intraperitoneal infusion of 5-fluorouracil. In a recently published article written by us, we did not register any tumour calcification following intraperitoneal administration of the same dose of 5-fluorouracil alone to a similar group of nine patients with colorectal liver metastases, and similar findings have been seen in a further 20 patients[5]. We think that it is more than merely a coincidence that tumour calcification appears in the first three patients treated with the addition of temporary dearterialization.

In our original manuscript six photographs of CT scans were included, showing all three patients. When Professor Anders Lunderquist reviews the floppy discs from the examinations and states that there is a regression of tumour growth in all three patients after institution of therapy, we believe him. We never judge tumour status from an individual X-ray photograph.

We do not claim any major benefit for the patients from this new treatment modality, but feel reassured by the appearance of some good prognostic signs to undertake a controlled clinical trial.

S. Bengmark

Department of Surgery
Lund University
S-221 85 Lund
Sweden

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Parotid tumours

Sir

We read with great interest Gunn and Parrott's article entitled 'Parotid tumours: a review of parotid tumour surgery in the northern regional health authority 1978–1982' (*Br J Surg* 1988; **75**: 1144–6). The authors are to be congratulated on their exposé of the unsatisfactory way in which parotid tumours are currently managed. Unfortunately, we suspect that similar figures would be obtained from most health authorities if similar surveys were to be undertaken.

We are particularly concerned that this paper should not be used as an argument against formal parotidectomy, and wonder if the authors would agree with our suspicion that the high incidence of incomplete excisions following formal parotidectomy in this series (15·8 per cent) is a reflection of lack of experience on the part of the surgeon rather than a criticism of the operation itself (43·8 per cent of operations were performed by surgeons whose experience did not exceed an average of one parotid tumour case per year). Our own experience[1] demonstrates that, with experience, complete excision can be obtained in almost every patient (however thin the margin of normal tissue surrounding the tumour) and this implies that all patients with a lump in the parotid region should be referred to a centre with a particular interest and experience in such problems. Only with this focusing of the clinical material will surgeons in training obtain the necessary skills and sufficient experience to improve on the currently unsatisfactory situation described in the paper in question.

Since approximately 60 per cent of recurrences are multiple[2], the optimal time to cure the patient of a pleomorphic adenoma is at the first operation. Failure to do so increases the likelihood that the patient will ultimately suffer permanent facial palsy as parotidectomy for recurrent tumours carries a substantially increased risk of facial nerve damage. Moreover, as long as any residual tumour remains the greater must be the chance of malignant change.

G. T. Watkin
M. Hobsley

The Middlesex Hospital
London W1N 8AA
UK

1. Stevens LK, Hobsley M. The treatment of pleomorphic adenomas by formal parotidectomy. *Br J Surg* 1982; **69**: 1–3.
2. Watkin GT, Hobsley M. Influence of local surgery and radiotherapy on the natural history of pleomorphic adenomas. *Br J Surg* 1986; **73**: 74–76.

Authors' reply

Sir

Thank you for showing us the letter by Professor Hobsley and Mr Watkins. We were pleased to note their interest in our paper and also noted their concern at the incidence of 15·8 per cent incomplete excisions for pleomorphic adenomas following formal parotidectomy. Whilst acknowledging the excellent results reported by Professor Hobsley, we still think that incomplete excisions will occur following conservative parotidectomy, particularly in tumours sited in the deep lobe, between the branches of the facial nerve or near the zygoma. All surgeons have 'learning curves' and even experienced surgeons will make mistakes. Similar reservations about complete excision of pleomorphic adenomas appear to be held by Conley[1].

Nevertheless, we agree that surgeons without a special interest in parotid surgery may wish to identify colleagues within their own, or other, districts to whom they would be happy to refer parotid tumours. It would seem that surgeons dealing with approximately from five to seven parotid tumours each year have a practice sufficient to produce good results[2].

A. Gunn
N. R. Parrott

Ashington Hospital
Ashington NE63 0SA
UK

1. Donovan DT, Conley JJ. Capsular significance in parotid tumour surgery: reality and myths of lateral lobectomy. *Laryngoscope* 1984; **94**: 324–9.
2. Hancock BD. Pleomorphic adenomas of the parotid: removal without rupture. *Ann Roy Coll Surg Eng* 1987; **69**: 293–5.

Book reviews

Current Operative Surgery: Urology

A. R. Mundy. 192 × 260 mm. Pp. 217. Illustrated. 1988. London: Baillière Tindall. £42.50.

This multi-author compilation from world renowned specialists within urology is clearly yet concisely written and illustrated with top class line drawings and photographs. It is undoubtedly designed for trained urologists who wish to enlarge their repertoire of operative procedures, particularly those wishing to embark upon reconstructive lower tract or radical cancer surgery.

Each of the 12 chapters outlines the preoperative assessment, results and complications of a particular procedure and describes the intimate operative details that the readership will demand. Despite its basic premise as a practical manual, this volume serves as both a good tutor of relevant preoperative investigation and an excellent supervisor of the scientific literature germane to each technique. Its continuity of style and presentation also invites the reader to delve into those chapters which might not, at face value, excite the greatest immediate interest.

This volume serves to emphasize the need for continuing general training in urology by demonstrating that a variety of organ systems may benefit from 'conventional' surgery whilst underlining the need for specialist endoscopic expertise. It is to be thoroughly recommended to its intended audience.

B. Ellis

Consultant Surgeon
Ashford
Middlesex
UK

Palliation in Malignant Disease

J. G. Mosley. 162 × 240 mm. Pp. 165. Illustrated. 1988. Edinburgh: Churchill Livingstone. £19.95.

Mr Mosley is to be congratulated on tackling this difficult subject with such a good reference background. The problem is that it is difficult to know who will read his work. He gives a subject-by-subject account of conventional treatment for various malignancies and then broad hints on how to manage the recurrent disease although not in as much detail as one would like. 'BCG vaccine, vaccinia virus or chemotherapy are useful palliative measures'—when and how often? As a reference for those who are not clinicians it may be helpful and if the library funds of a large district general hospital are flush perhaps this book may be justifiably purchased.

M. Perry

Consultant Surgeon
Portsmouth
UK

Care of the Critically ill. Third edition

S. M. Ayres, A. Schlichtig and M. J. Sterling. 177 × 252 mm. Pp. 404. Illustrated. 1988. London: Wolfe Medical. £25.00.

This revised edition aims to describe the 'science and art of critical care' and provides a basic textbook for those involved in the care of patients on intensive therapy units. The book is readable and although not written specifically for surgeons should be of interest to those not already fully *au fait* with the overall management of seriously ill surgical patients.

The fundamentals of cellular metabolism, cardiovascular, respiratory and renal physiology and the pathophysiological changes that occur in response to injury and disease are clearly described. The authors' view on the current optimal treatment of the critically ill is given with appropriate justification. In addition there are chapters on multiple organ failure, the central nervous system and nutritional alterations that occur in these patients, specific aetiological factors (including sepsis, burns, trauma and AIDS), and an overview of the organization of critical care. The illustrations are good, but brief summaries at the end of each section or chapter would have been helpful.

The book was originally based on experience with cardiac surgery patients which may explain its bias away from the general surgical patient. There is no discussion of the surgical aspects of management. The role of sepsis, particularly intra-abdominal infection, is neglected, and its investigation and management are not covered. The pathophysiological effects of endotoxaemia and its importance in 'septic' patients is barely mentioned.

Despite these reservations the book can be recommended as a basic non-surgical text for those surgeons involved in care of the critically ill.

J. N. Thompson

Lecturer in Surgery
St. Mary's Hospital
London W2 1NY
UK

A Colour Atlas of Trans-abdominal Gastric Fundoplication

J. G. R. Cumming. 265 × 196 mm. Pp. 61. Illustrated. 1988. London: Wolfe Medical. £19.00.

The Wolfe series of atlases of single surgical procedures is probably familiar to most surgeons by now. I must confess that I often find colour photographs of operative surgery disappointing as a guide for technique. Fine detail may disappear in a sea of red and the photographs have to be well chosen and properly composed to make the point at each stage. Fortunately most of the illustrations in this book are exceptionally clear. There are also a few line drawings which complement the colour plates well and there is no doubt at all about the procedure being performed. I also enjoyed the introductory section on diagnosis and preoperative assessment, which is concise, up-to-date and reasonably practical.

There is, however, one major defect of this book. The authors have chosen a variation of the Nissen fundoplication which is individual and rather dated. Most oesophageal surgeons now accept that the 'floppy' version of the Nissen described by Donahue and Bombeck 11 years ago is an essential modification to reduce the side effects of dysphagia and gas bloat. A fundamental problem of all surgery for gastro-oesophageal reflux is that it is inherently variable and this affects the end results. A monograph on the Nissen which ignores the variations is not, in my opinion, a good guide for the trainee.

J. Bancewicz

Senior Lecturer in Surgery
Hope Hospital
Manchester
UK

Lecture Notes on General Surgery. 7th ed.

H. Ellis. 137 × 24 mm. Pp. 459. Illustrated. 1987. Oxford: Blackwell Scientific. £9.95.

Reviewing a 'classic' undergraduate textbook is not easy since thousands of students have voted with their feet and can attest to its worth. To see how the seventh edition has changed, I reached for my first edition, dated 1965. At first sight hardly anything seemed to have changed apart from the addition of two chapters. The first addition deals with postoperative fluid and electrolyte balance and perioperative nutrition, the other with transplantation surgery.

Since the first edition typographical errors have been corrected and when new developments occurred, for example the introduction of H_2 antagonists and highly selective vagotomy in the field of peptic ulceration, they have been added to existing text rather than a full rewrite to give a new perspective. Thus, surgery for peptic ulcer is relatively overstressed compared with medical treatment and within the surgical discussion gastrectomy is still overemphasized compared with vagotomy. Also, there is no mention of mucosal defence mechanisms in the aetiology of peptic ulceration, and drugs which are non-antisecretory but highly effective at healing ulcers are omitted. Other inappropriate lack of emphases include the role of sclerotherapy for oesophageal varices and transurethral resection for prostatic hypertrophy.

Unfortunately this seventh edition reads as though it was written at the time the sixth edition was produced—in 1983. If this book is to remain a 'classic' for the aspiring student, a radical rewrite will be necessary to get rid of the dead wood rather than simply grafting a few new sentences for each new edition. One of the few examples in the book where an update has been successful is the extensive additions to the section dealing with breast cancer. Perhaps the distinguished authors will consider taking on board a new recruit to edit the next edition.

R. F. McCloy

Consultant Surgeon
University Department of Surgery
Manchester Royal Infirmary
Manchester M13 9WL
UK

Postmastectomy Reconstruction. Second edition

T. D. Gant and L. O. Vasconez. 174 × 258 mm. Pp. 298. Illustrated. 1988. Baltimore: Williams and Wilkins. US$68.95

There will be those who view a publication like this as an enjoyable essay into surgical extravaganza without relevance to modern management of breast cancer. After all, we all know that mastectomy belongs to a bygone age and that conservation is all the rage: except, of course, for the patients who prefer it, for the lesions not suitable for local excision on grounds of size or position, for treatment of local recurrence after conservation therapy and for the few cases where prophylaxis is required. No wonder there has been a need for a comprehensive volume on postmastectomy reconstruction, not just for plastic surgeons but, I would suggest, any surgeon interested in obtaining the best outcome for the patient. But is this the book?

Gant and Vasconez have assembled 20 contributors to write 20 chapters in 298 pages. The chapters vary in their value—the early chapters on philosophy, primary treatment, outcome and aetiology hardly do justice to the enormous literature on these subjects and it is sad to see a continued belief in the value of 5-year survival as an indicator of outcome in early disease. Michael Lagios has provided a workmanlike review of the pathological features of breast disease. The chapter on arterial blood supply considers veins, lymphatics and nerves but physiology doesn't deserve a mention. The meat of the book lies in its handling of matters related to reconstruction. I particularly enjoyed the chapters on breast implants by Boyd Burkhardt, tissue expansion by Gibney, and Jarrett's chapter on prophylactic mastectomy because of its honest attempt to discuss the complications. Those not familiar with the latissimus dorsi, thoracoepigastric and transverse rectus flaps will find these sections helpful but they will be of limited value to established plastic surgeons who may find more in the chapters on topology, and the description of less commonly used techniques such as the upper rectus flaps, free grafts and breast shaving. The management of the contralateral breast is dealt with in a reasoned manner; the chapter on nipple areola complex reinforces my belief that when a lot of procedures are used with the same objective none of them is entirely satisfactory.

Overall the book is good on the 'how', although some of the illustrations (all in black-and-white, mostly photographs with some line drawings) lack quality of reproduction. It is less good on the 'when and why' to do reconstruction and on which procedure to choose. Regrettably no attempt has been made to grapple with the difficult but vital aspects of patient views on the results of this type of surgery—perhaps the next edition will put this right.

This book will appeal mainly to the surgeon with an interest in breast disease who either performs reconstructive surgery or who wants to refer patients for it. It represents a good state-of-the-art essay on the available techniques.

D. J. T. Webster

Surgical Consultant
Llandough Hospital
Cardiff
UK

Patient Care in Vascular Surgery

J. W. Hallett. 134 × 214 mm. Pp. 306. Illustrated. 1987. Edinburgh: Churchill Livingstone. £16.50.

This chunky paperback is intended to be a practical guide for students, residents, technicians and nurses. It encompasses arterial and venous, but not lymphatic, disease. The rapid rate of progress made in vascular surgery has necessitated extensive revision of this second edition and it is up to date. The condensed but readable text contains a mass of information and each chapter has an extensive bibliography. Anatomy and pathology are very briefly mentioned. The strong points are patient assessment, practical management and postoperative care. It is well organized, with headings, tables, diagrams, line drawings and graphs.

The emphases are slightly different from those one might expect in the UK: almost nothing on the recording of patient histories and differential diagnosis; a 26-page chapter on laboratory tests; relatively slight attention to venous disorders; a greater willingness to operate on claudicants and patients with asymptomatic carotid lesions. However, one suspects that these trans-Atlantic differences are becoming much less marked than even 5 years ago. This is the sort of book that should lie around on the desk or coffee table and be well thumbed wherever vascular surgery is practised.

C. V. Ruckley

Consultant Surgeon
The Royal Infirmary
Edinburgh EH3 9YW
UK

Surgery Annual 1988

L. M. Nyhus. 167 × 240 mm. Pp. 355. Illustrated. 1988. East Norwalk, Connecticut: Appleton and Lange. US$69.95.

There are 16 chapters in this annual review, 11 from North America, three from the UK and one each from Sweden and France. This year there seems to be a particular emphasis upon gastrointestinal surgery, but, as always, there is considerable variety in the topics covered and there is likely to be something of interest for all surgeons.

There is an excellent review of the management of portal hypertension by Rykers who is a firm proponent of the distal splenorenal shunt. He suggests that patients with poor results usually reflect the inexperience of the surgeons performing the operation, but from previous experience many surgeons would be wary of such a conclusion having heard a similar claim made for other procedures that were ultimately found to be inherently faulty.

Warshaw and Schapiro provide a very complete review of the relationship between pancreas divisum and pancreatitis, concluding that obstructive pancreatitis occurs only in patients with pancreas divisum who have stenosis of the accessory papilla. They are able to achieve dorsal pancreatography in 90 per cent of patients which is much higher than the reviewer's experience. To support their contention that it is the combination of stenosis of the accessory papilla with pancreas divisum that is responsible for the dorsal pancreatitis, they emphasize the rarity of pathological changes in the anatomy of the dorsal duct accompanying anomalous changes. Their diagnosis of obstructive pancreatitis rests mainly upon the test that they have devised which records changes induced by secretin in the ultrasonic diameter of the dorsal pancreatic duct and they review in a very reasonable manner their extensive experience. This chapter should certainly be read by surgeons treating patients with unexplained abdominal pain.

Bismuth and his colleagues describe the development of segmental resection of the liver to which they have contributed so much. Classical resections in which excessive amounts of normal parenchyma may be removed are being replaced by segmental excisions based upon portal and arterial blood supply. Although the surgical resections involved are well described, as the authors emphasize, peroperative ultrasonography is an essential component of segmental excision and I would have preferred more illustrations of this technique in this chapter.

Bengmark and Jeppsson describe their 20-year experience of various forms of hepatic arterial ligation in the treatment of hepatic tumours. They recognize that the results have been disappointing and suggest that the major reason for this is the development of arterial collaterals. However, they conclude enthusiastically with their initial results of repeated transient de-arterialization using a balloon occluder.

Cahill and Pain review renal failure and other complications produced by endotoxin in obstructive jaundice. This is a useful review but from the content I suspect that it was written in the latter half of 1986 and since then there has been more interesting work in this field. During the next decade major developments will be made in the investigation and treatment of disorders of gastrointestinal motility.

Pellegrini and Allegra provide an up-to-date review of gastric emptying and the problems encountered in surgical patients.

In their chapter on 'Respiratory function in surgical patients', Pett Jr and Wernly remark 'the quality of care . . . varies among physicians. It is refreshing to see residents and surgeons continue to resist transferring the responsibility of peri-operative management to specialists'.

I concur with the concept that a patient is admitted under the care of a single clinician who must be responsible for all major decisions and with the concept that surgeons must be knowledgeable about the function of all organs in the body. However, changes in pulmonary and cardiac function can occur with dramatic suddenness, particularly in the postoperative period, and may require instantaneous treatment. Many surgeons would be unhappy to transfer the ultimate responsibility of care for their patients but would be happy to share responsibility, particularly in fields where there may be individuals with more expert knowledge.

I enjoyed reading this, the twentieth volume, of this well known book. The topics chosen by Professor Nyhus for this edition were provocative and pertinent.

D. E. F. Tweedle

Consultant Surgeon
Withington Hospital
Manchester M20 8LR

Notices and announcements

29–31 March 1989
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information: The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

6–9 April 1989
4th ASEAN Otorhinolaryngological Head and Neck Congress
Singapore
Information: Dr R. E. Stanley, Organizing Secretary, c/o ENT Department, Singapore General Hospital, Singapore 0316

22–28 April 1989
Critical Care in the 1990s
Aruba, Dutch Caribbean
Information: Dr Omar Prakash, Thorax Centre, Erasmus University, PO Box 1738, DR Rotterdam, The Netherlands

18 May 1989
Debate: Balloon and Laser Angioplasty will Reduce the Necessity for Vascular Surgery
London, UK
Information: Mr John Wolfe, St. Mary's Hospital, The Queen Elizabeth Queen Mother Wing, Cockburn Lecture Theatre, Praed Street, London W2 1NY, UK

24–27 May 1989
8th Annual Meeting of the American Association for Cancer Research
San Francisco, California, USA
Information: American Association for Cancer Research, 530 Walnut Street, 10th Floor, Philadelphia, Pennsylvania 19106, USA

25–26 May 1989
International Symposium: Surgery in Europe
Rome, Italy
Information: Professor Sergio Stipa, V Clinica Chirurgica, Policlinico Umberto I, Viale del Pliclinico, 00161 Rome, Italy

4–17 June 1989
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information: Dr J. F. Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 13214, USA

12–13 June 1989
Cholelithorama: Total Gallstone Management
London, UK
Information: BDI Conferences Ltd., 3 Beaconsfield Terrace Road, London W14 0PP, UK

19–21 June 1989
Tripartite Meeting
Birmingham, UK
Information: Mr Roger Grace, The Royal Hospital, Wolverhampton, UK

21–23 June 1989
71st Annual Meeting of The Endocrine Society
Seattle, Washington, USA
Information: The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

24–27 June 1989, 28–30 June 1989
Second Mediterranean Surgical Congress
Athens, and continued in Heraklion, Crete, Greece
Information: Ms Peggy Alexopoulou, Public Relations Centre, 56 Hippocratous Street, 106 80 Athens, Greece

2–15 July 1989
Neonatal and Paediatric Surgery
Manchester, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

13–15 July 1989
XIVth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

15–16 July 1989
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

21–24 August 1989
4th International Symposium on Obesity Surgery
London, UK
Information: Mr E. R. T. C. Owen, Academic Surgical Unit, The Queen Elizabeth Queen Mother Wing, St. Mary's Hospital, Praed Street, London W2 1NY, UK

27 August–1 September 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Informtion: International Congress and Convention Association, PO Box 50006, Tel Aviv 61500, Israel

6–8 September 1989
Fourth World Congress of the International Society for Diseases of the Oesophagus
Chicago, Illinois, USA
Information: 4th World Congress of the International Society of Diseases of the Oesophagus, 911 Busse Highway, Park Ridge, Illinois 60068, USA

10–15 September 1989
3rd International Symposium on Inflammatory Bowel Diseases Jerusalem, Israel
Information: International Congress and Convention Association, P.O. Box 5006, Tel Aviv 61500, Israel

10–15 September 1989
Trauma Surgery
Belfast, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

21–23 September 1989
Annual General Meeting of the Association of Surgeons in Training
Cardiff, Wales, UK
Information: Mr B. Taylor, Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

16–19 October 1989
Second International Conference on Melanoma
Venice, Italy
Information: Dr Mario Santinami, Vice Secretary General, Scientific Programme Committee, Instituto Nazionale Per Lo Studio e La Cura dei Tumori, 20133 Milano, Via Venezian 1, Italy

10–16 September 1989
33rd World Congress of Surgery Toronto, Canada
Information: 33rd World Congress of Surgery, Congress Canada, Congress Management, 73 Richmond Street West, Suite 300, Toronto, Canada M5H 1Z4

15–17 November 1989
Fourth EORTC Symposium on Advances in Gastrointestinal cancer: Research and Treatment
Strasbourg, France
Information: J. P. Arnaud MD CMCO, 19 rue Louis Pasteur, Schiltigheim BP 120, 67042 Strasbourg Cedex, France

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr Joseph W. C. Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

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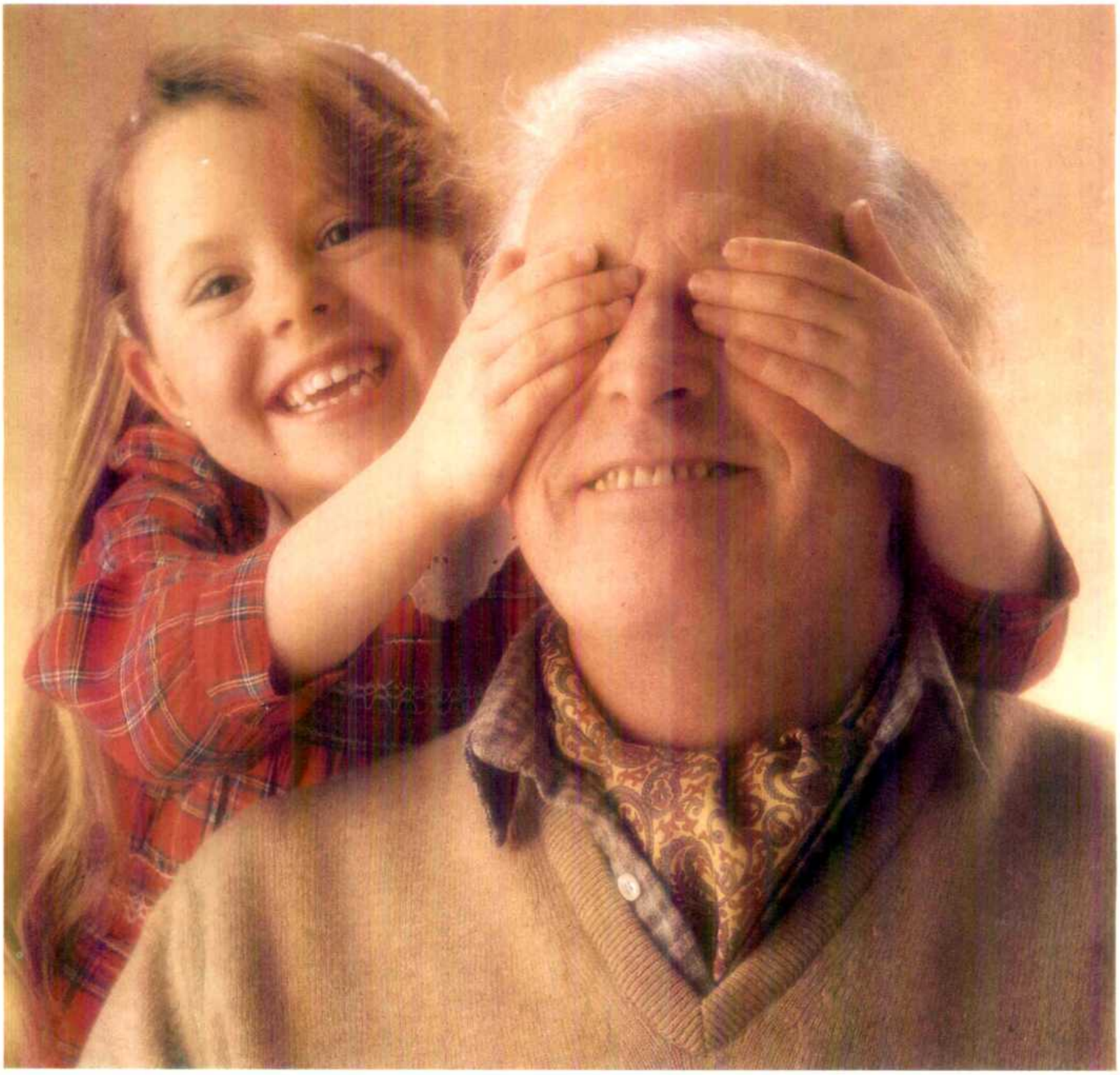
The British Journal of Surgery

Volume 76, Number 4, April 1989

Guess which prostate cancer treatment most patients would choose.



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Reference 1. Lunglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex'– a new treatment for prostatic cancer. International Congress and Symposium Series.* 125. London: RSM Series, 1987: 47-51.
2. Peeling W B. ibid: 27-46.

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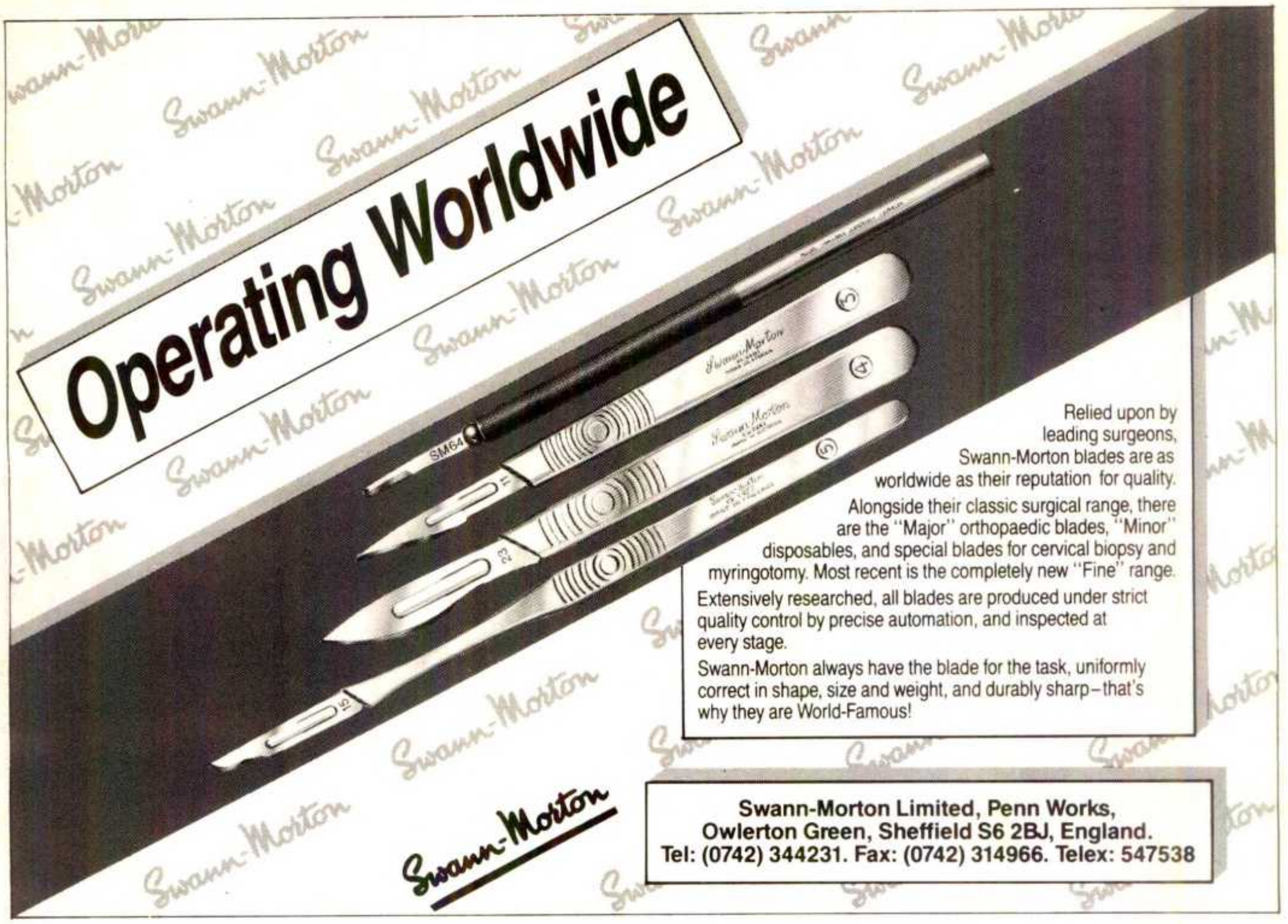

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A perspective for the management of variceal bleeding

The 1980s have seen a major expansion in therapies available for the prevention of recurrent variceal bleeding. Drug therapy[1], endoscopic sclerotherapy[2], and liver transplantation[3] have greatly extended the range of options beyond the previously available surgical methods of total portal–systemic shunts, selective variceal decompression, and devascularization procedures. The dilemma which the clinician now faces is how to choose the right therapy for the right patient at the right time. This article summarizes the practice and philosophy which have evolved at Emory University Hospital in this decade with the availability of all modern methods of treatment.

The major questions to be addressed are, firstly, what is the patient's risk of rebleeding and developing liver failure and, secondly, what is the risk of rebleeding and liver failure with the alternative methods of treatment? The first question requires complete evaluation of the patient and the second a knowledge of the outcome when each method is used to treat patients with different aetiologies and stages of cirrhosis.

Patient evaluation will assess rebleeding risk primarily by endoscopy: larger variceal size and endoscopic risk factors such as red wale markings and cherry-red spots are indicative of increased risk of rebleeding. Angiographic assessment of portal hypertension with venous phase visceral arteriography will demonstrate variceal inflow paths while wedged hepatic vein pressure will measure the degree of portal hypertension. The aetiology of the portal hypertension will influence the outcome from variceal bleeding; for example, patients with portal vein thrombosis have a much better prognosis than those with cirrhosis. In the patient with cirrhosis, a combination of clinical and laboratory parameters as used in Childs' classification provides a useful working definition of severity. However, a more profound judgement of the stage of the liver disease can be achieved from knowledge of the morphological status at liver biopsy, measurement of liver volume, and measurement of hepatocyte function, e.g. by galactose elimination capacity. The important differentiation is to distinguish between patients with reversible disease (alcoholic or chronic active hepatitis) and those with end-stage cirrhosis. Therapy for these subsets will differ.

The major points emerging from reported studies of the available methods of treatment as interpreted by this author are as follows. Propranolol has established a place in the prevention of the first bleeding episode: it will reduce portal hypertension[4]. Propranolol may also have some benefit in reducing rebleeding in good-risk alcoholic patients and in patients with portal hypertensive gastropathy[1]. Endoscopic variceal sclerosis is a widely applicable therapy but has a 30–60 per cent rebleeding rate and an ultimate failure rate of 15–30 per cent: it has no adverse effect on liver function[2,5]. Total portal–systemic shunts will control bleeding, but have an unacceptably high rate of hepatic failure; they are best tolerated by the patient with alcoholic cirrhosis[6]. Selective variceal decompression has a bleeding control rate as good as that achieved by total shunts ($\geqslant$90 per cent), and is associated with better maintenance of hepatic function: its physiological goals are best achieved in patients with non-alcoholic disease. Devascularization procedures have a significant rebleeding rate (up to 40 per cent) and maintain hepatic function but require follow-up endoscopic surveillance. Liver transplantation treats both the portal hypertension and the hepatic failure in patients with end-stage disease. It can be achieved with an acceptable mortality and is a viable therapeutic option.

The current problem is, therefore, how to use these therapies to best advantage in optimal patient care. The current management scheme which has evolved in our practice is as follows[5]. The patient should be resuscitated and stabilized after the acute bleeding episode; the use of sclerotherapy at this time has markedly reduced the need for Pitressin® (Parke Davis Medical, UK) and/or tamponade. Complete patient evaluation, based on the outline given above, can be completed over the next 3–4 days. In patients with cirrhosis, chronic sclerotherapy is a rational first-line treatment[5]. We consider that this should be carried out by, initially, frequent (weekly or bi-weekly) sessions until variceal obliteration is achieved, followed by less frequent surveillance/therapy sessions. Exceptions to this line of management are made for: (1) good-risk patients (Childs' A, galactose elimination capacity >300 mg/min) in whom the 30–60 per cent rebleeding risk of sclerotherapy may be unacceptable (we

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consider that such patients should be offered a distal splenorenal shunt); (2) patients with portal vein thrombosis, who can expect a normal lifestyle and expectancy after a successful distal splenorenal shunt; and (3) patients with gastric varices or portal hypertensive gastropathy not amenable to sclerotherapy (we consider that they should have surgery).

When variceal bleeding is controlled by sclerotherapy, continued monitoring of the liver disease is an essential component of further management. In many patients, control of bleeding and stable disease combine to give a return to a normal lifestyle. In some patients, progression of disease may ultimately lead to liver transplantation.

When variceal bleeding is not controlled by sclerotherapy, further therapy is largely dictated not only by the bleed itself but also by the underlying disease. The definition of a sclerotherapy failure is the most vexing question in this field at the present time. Such treatment failure cannot be decided solely by the number of rebleeding episodes or the blood transfusion requirement. At one end of the spectrum a patient who dies from a single rebleeding episode is clearly a sclerotherapy failure, while at the other end is a patient who has numerous rebleeding episodes which are readily controlled by further sclerotherapy and who ultimately achieves freedom from further bleeding. Sclerotherapy failure must rather be decided by (1) the overall rebleeding pattern taking into account the severity and site of rebleeding and any mucosal changes and (2) the life-threatening nature of further bleeding, which may be dictated not only by the bleed itself but also by factors such as geographic remoteness, patient compliance with treatment and underlying disease severity.

When the patient and clinician believe that sclerotherapy is no longer adequate therapy, we consider that good-risk patients should be managed by a distal splenorenal shunt and poor-risk patients considered for transplantation. Data from our randomized study comparing distal splenorenal shunt with sclerotherapy show that successful surgical salvage of sclerotherapy failures leads to the best survival statistics in the group originally randomized to sclerotherapy[5]. In this study one-third of patients ultimately failed on sclerotherapy because of rebleeding; half of these rebleeds occurred in the first few months with a second peak after 2 years. In most patients sclerotherapy buys the time to allow individuals to declare the natural history of their disease, and gives the clinician the time to make a logical decision on further therapy.

Total portal–systemic shunts in our practice are limited to life-saving 'salvage' operations in the patient with continued massive acute bleeding. In this setting our preference is for a large bore (16 mm) interposition portacaval shunt. Devascularization procedures are only used in patients in whom there are no veins suitable for selective shunt and in whom bleeding is not controlled by sclerotherapy, usually because it is from gastric varices. This option is preferred to total shunt in the elective setting, particularly when followed by surveillance endoscopy and/or sclerotherapy.

In summary, there have been major changes in the field of therapy available for variceal bleeding in the past decade. In our practice approximately 100 new patients are referred each year for definitive therapy to prevent recurrent variceal bleeding. The breakdown of definitive methods used approximates as follows: sclerotherapy, 50 patients; distal splenorenal shunt, 40 patients; transplantation, ten patients. Propranolol will be used as adjunctive therapy in a minority of these patients. Other surgical procedures will be used in urgent cases, and occasionally for unusual problems. However, practices change and evolve. By the year 2000 . . . ?

J. M. Henderson

Emory University Hospital
Atlanta
Georgia USA

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Tamoxifen comes of age

Invasive breast cancer, once it has become palpable, is a potentially fatal disease. Malignant cells are likely to have seeded by vascular and lymphatic routes and to have formed 'micrometastases' in systemic sites and in regional lymph nodes. Because of the slow-growing nature of the disease it may be many years before these micrometastases become clinically manifest; nevertheless, once the disease has spread systemically local treatment, no matter how radical, cannot be curative. There is good evidence that there is a threshold of size at which invasive cancer is likely to have metastasized. From histopathological studies[1] this was initially believed to be 0·5 cm, but more recent information related to mammographic screening suggests that 1·0 cm is a more reasonable estimate[2]. It is in the detection of the small invasive (as well as the non-invasive) cancers that mammographic screening has most to offer, and there is now adequate evidence that screening reduces the number of deaths.

But what of the larger invasive tumours for which systemic therapy offers the only real hope of long-term cure? One form of systemic therapy is tamoxifen, a substituted triphenylethylene compound, the antioestrogenic effects of which were first described by Harper and Walpole[3] in 1966. Its value in women with advanced breast cancer (both local and systemic) is now firmly established. Remission is induced in 30–40 per cent of women to whom it is administered as first-line therapy. In controlled randomized trials its action was found to be similar to that of pharmacological doses of diethylstilboestrol, but unlike stilboestrol it had no troublesome side-effects. For this reason it is now not only the agent of choice for those patients who develop so-called recurrent disease but is appropriate adjuvant therapy in primary disease.

Adjuvant therapy

It is now confirmed that adjuvant tamoxifen benefits women over 50 years of age with primary breast cancer[4]. A recent over-view pooling the results of 28 separate randomized trials, which included more than 16 000 women (3782 deaths), has indicated that tamoxifen given for 1–2 years reduces the annual mortality rate by (mean ± s.d.) 16 ± 3 per cent, a highly significant fall. In women over 50 years of age the reduction was 20 ± 3 per cent; in absolute terms this represents an increase in survival at 5 years from 68 to 73 per cent, a difference of 5·7 ± 1·0 per cent. A beneficial effect was observed in both node-negative and node-positive women of this age group but was not observed in women younger than 50 years of age. However, the number of younger women was small and most had also received adjuvant chemotherapy in both arms of the trials.

It is relevant to ask whether the administration of tamoxifen as immediate adjuvant systemic therapy has any advantage to its delayed use for recurrent disease. This question has been addressed in the Scottish tamoxifen trial[5] in which 1312 evaluable patients with primary cancer (242 premenopausal women without proven node involvement and 1070 postmenopausal women with negative and positive nodes) were treated by mastectomy and randomized to receive immediate tamoxifen (20 mg daily) for 5 years or to be controls. In the control group tamoxifen was to be given on recurrence of disease and this has been first-line therapy in more than 90 per cent of such patients. A highly significant effect of immediate tamoxifen therapy on survival and on recurrence-free survival was still observed. This effect occurred not only in postmenopausal women with negative or positive nodes but also in premenopausal women with negative nodes. A recent report from the USA supports this finding in node-negative (and oestrogen-receptor positive) disease[6]. A subset of 104 women separately randomized for the pilot study preceding the trial have all been followed up for more than 5 years, and the reduction in the 5-year mortality rate approximates to 40 per cent. It is important to know whether or not tamoxifen should be administered for the rest of the patient's life and a second randomization is now being carried out at the end of the 5-year period, women being allocated either to continue or to stop taking the drug. This is a most important addition to the study.

Pharmacological action

Tamoxifen acts by competitive inhibition of the binding of oestrogen by its receptor. Unlike the oestradiol–receptor complex, the tamoxifen–receptor complex is ineffective and fails to stimulate the genome. In advanced disease there is a good relationship between the oestrogen receptor status of the tumour and the response to therapy. The relationship between oestrogen receptor status and the reduction in mortality achieved by adjuvant tamoxifen is being examined in several trials. A recent analysis of the Scottish trial suggests that while there may be a trend in favour of patients with oestrogen receptor-rich tumours (>100 femtomoles oestrogen receptor per

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milligram protein) having a greater reduction in risks of mortality and recurrence than those whose tumours are receptor-poor or negative, this is not significant (H. J. Stewart, personal communication). This finding is in accord with the report of the NATO trial[7] but not with that from Denmark[8]. Further study is required.

Patients who will benefit

It is clearly important for cost-effectiveness that tamoxifen should not be given to patients who are unlikely to benefit from its use. The over-view of trials referred to above also considered the results of 31 trials (9069 women) in which chemotherapy was given to one arm. A significant reduction in the annual mortality rate was again observed, and was highly significant in women under the age of 50 years. Should such women not be responsive to tamoxifen (and more information is required to clarify the potential benefit of tamoxifen in this age group) they should not be denied chemotherapy, which is best given as CMF (cyclophosphamide, methotrexate, 5FU).

In patients with primary disease, the tumour in the breast is the only available monitor of the effectiveness of systemic treatment. It is logical to suggest that trials should be instituted in which systemic therapy is the first treatment given, local therapy being reserved until the response of the tumour has been assessed. This is a policy that we are studying in large, but still operable, primary tumours[9], and which is also our preferred option in elderly and frail patients with primary disease. Two randomized controlled studies have now been reported indicating that the initial use of tamoxifen in such elderly patients (reserving surgery for the non-responding tumour) does not compromise survival[10,11]. Our current policy is to assess both the response to tamoxifen and the need for local therapy at 3 months.

The logic of this approach is strengthened by the availability of fine needle aspiration cytology. Not only can the diagnosis of cancer be confirmed but histochemical assays of oestrogen receptor (and if desired other parameters of cell type and function) can be performed. In our elderly patients with primary tumours, the relationship between immunohistochemical assays for oestrogen receptor and the response to tamoxifen has proved to be encouraging. In a series of 52 patients, only one of 21 tumours with less than 25 per cent of the cells staining for receptor in fine needle aspirates responded by a reduction in tumour size following tamoxifen treatment (D. J. Gaskell, R. A. Hawkins, K. Sangster, A. P. M. Forrest, manuscript in preparation).

It would appear that tamoxifen, with its absence of side-effects, is the systemic treatment of choice for primary breast cancer. However, this is so only in those patients likely to benefit: the next step must be to define who these patients are. Until a laboratory test to do so has been validated, it would appear reasonable, at least in selected patients, to test the efficacy of the drug before removal of the only measurable sign of disease, that is the primary tumour.

A. P. M. Forrest

University of Edinburgh
Edinburgh
UK

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Recessive mutations and chromosome deletions leading to cancer

J. Berne*, I. McColl and M. Adinolfi*

Department of Surgery and
**Paediatric Research Unit, Division of Medical and Molecular Genetics, United Medical and Dental Schools of Guy's and St. Thomas' Hospitals, Guy's Campus, London Bridge, London SE1 9RT, UK*
Correspondence to:
Professor I McColl

This review examines the effect that a small chromosome deletion affecting a specific DNA sequence may have in producing a state of 'hemizygosity' for a gene or genes, and so triggering malignancy of the cells concerned. The association between such deletions and a variety of cancers will be considered and the implications for clinical practice will be outlined.

Keywords: Cancer, chromosome deletions, oncogenes

The involvement of genetic factors in the aetiology of cancer was first clearly stated by Boveri in 1914[1], who had observed that abnormalities of the mitotic cycle of sea urchin eggs frequently preceded abnormal growth. Later, in 1930, Winge[2] suggested that a population of cancer cells represents the result of a single genetic event, and proposed the 'stem cell' concept. Many years had to pass before cytogenetic[3,4] and biochemical analysis[5] of cancer cells made it possible to demonstrate conclusively that all cells of a tumour are cloned from a single cell and that, in the course of their proliferation, they may acquire new characteristics and ultimately differ from the parental cells.

The concept that tumorigenesis is a multistage process, which involves changes at gene level, has gained new emphasis with the discovery of the oncogenes and their role in the transformation of normal cells[6,7].

The purpose of this article is to review briefly a single aspect of the association between chromosome abnormalities and cancer: the effect that a small chromosome deletion may have in producing a state of 'hemizygosity' for a gene (or genes), thus triggering malignancy of the affected cells. These recent discoveries have been made possible by the collaboration of oncologists, surgeons and geneticists as many of these small deletions can only be detected when genetic probes are used to test freshly collected cancer cells. Awareness of the unique chromosome deletions associated with each type of cancer and a close working relationship between oncologists, surgeons and geneticists should improve diagnosis and prognosis of cancer patients and, at least in some cases, allow for more effective prevention of the disease in their relatives.

Major types of chromosome abnormalities in cancer cells

At present, several types of chromosome abnormalities have been shown to be associated with cancer (*Table 1*). The most frequent are: (a) reciprocal translocation with or without apparent loss of DNA sequence; (b) non-reciprocal translocation with loss of genetic material; (c) duplication or amplification of chromosomal DNA sequences; (d) deletion of a small chromosome segment resulting in hemizygosity of an allele at one locus[8,9].

Before discussing this last type of abnormality, we will briefly analyse a few examples of the other genetic defects.

Chronic myeloid leukaemia was the first disorder found to be associated with a reciprocal chromosome translocation with no apparent loss of DNA sequence. About 90 per cent of chronic myeloid leukaemia patients have a population of lymphocytes with a small chromosome, 'Philadelphia' (Ph^1), which results from the translocation of a segment of the long arm of chromosome 22 to, usually, chromosome 9. Appreciable loss of DNA in these leukaemic cells could not be detected by conventional techniques[10–14].

Several other types of leukaemia have been shown to be characterized by unique reciprocal translocations[9,15,16]. In acute promyeloblastic leukaemia, for example, the translocation involves the transfer of the short arm (p) of chromosome 15 to the long arm (q) of chromosome 17: $t(15p+;17q-)$. In acute myelogenous leukaemia the defect involves a translocation between chromosome 8 and 21: $t(8q-;21q+)$.

Perhaps the most investigated tumour involving a translocation is Burkitt's lymphoma, where the translocation occurs between chromosome 8 and either chromosome 14, 2 or 22, carrying respectively the genes for the heavy (14) or light (2 and 22) chains of the immunoglobulin gene[13,16,17]. The breakpoints of some of the reciprocal translocations observed in human carcinoma are often very near an oncogene. This has lent support to the hypothesis that, in these patients, tumorigenesis results from the activation of an oncogene, but how this occurs has not yet been established[16].

In some of these reciprocal translocations, genetic material is lost to a varying extent. Other tumours are characterized instead by a duplication of a chromosome or part of it. In many cases, duplications are seen in cancer cells from patients at the terminal phase of their disease, such as in patients with chronic myeloid leukaemia, where, in addition to the Ph^1 chromosome, an extra chromosome 8 or segments of chromosome 17 can be identified by cytogenetic analysis. Partial trisomies have also been observed in solid tumours[8], probably as a result of repeated mitotic abnormalities. As it is not possible to identify a uniform pattern of duplication of DNA segments in these cancers, the present view is that the genes involved in the duplications are not cancer-specific. Consistent with this suggestion is the fact that patients with trisomies of (or part of) chromosomes 8, 9 and 18 do not show an increased incidence of cancer[8]. An exception

Table 1 *Examples of chromosomal abnormalities in human cancer cells*

Abnormality	Examples and comments
Point mutation	Cancer of bladder and several other tumours
Deletion	Retinoblastoma, Wilm's tumour, cancer of lung
Translocation	Burkitt's lymphoma, and at least ten other different cancers
Inversion	Usually associated with other abnormalities
Amplification	Neuroblastoma: double minutes
Breakages, duplication, trisomies	Usually observed in advanced stages of neoplasms

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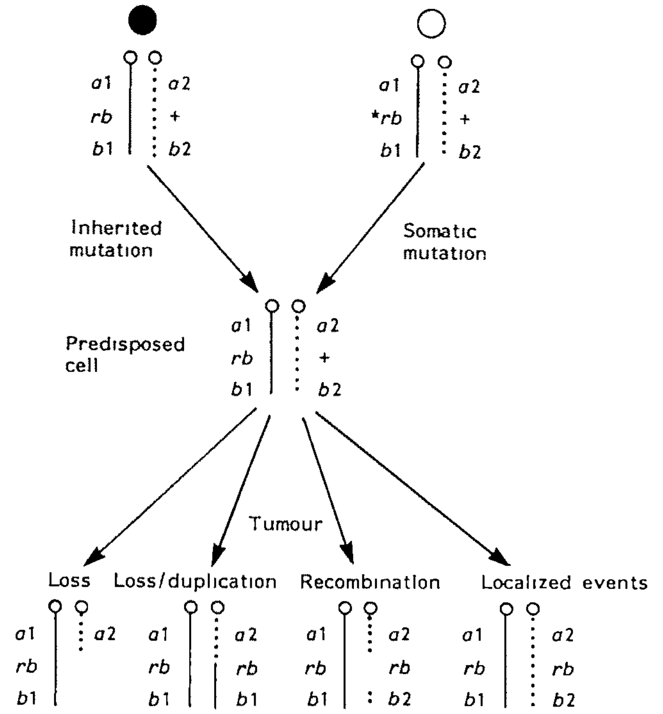

Figure 1 *Schematic mechanisms which can unmask a recessive gene* (rb) *predisposing for retinoblastoma. Patient* ● *has inherited the abnormal gene* (rb), *while patient* ○ *has acquired it in some cells by somatic mutation. Loss of part of the chromosome containing the normal gene* (+) *and a closely linked gene* (b2) *results in hemizygosity for the abnormal* rb *gene. Loss followed by duplication results in the presence of two copies of the* rb *gene A recombination event may also duplicate the* rb *gene Finally, a localized mutation may be responsible for the loss of the normal* (+) *gene, leaving the cell with two* rb *genes In all these instances the regulatory influence of the normal gene* (+) *on the* rb *gene is lost, resulting in cancer of the affected cell. DNA sequences at some distance from the inherited mutation* (*e.g. sequence for* a *or* b *loci*) *defined by restriction fragment length polymorphism can be employed to detect the deletion of the 'cancer' gene*

is trisomy 21, as patients with Down's syndrome have an increased predisposition to leukaemia or other haematological disorders[18,19].

Other duplications are unique to certain types of tumours. For example, neuroblastoma cells may contain several small chromosome segments with unique staining properties. Referred to as homogeneously staining regions or double minute segments, they contain multiple copies of several genes or even a single gene, often conferring resistance to drugs[8,20]. Duplication of oncogenes in double minute segments has also been shown to take place[17,21,22], and this, for example, has been held responsible for causing malignancy in patients with neuroblastoma.

DNA deletions and cancer

The fourth type of abnormality observed with increased frequency in cancer cells is a small deletion affecting a specific DNA sequence. This abolishes the state of heterozygosity of the cell for allelic genes at one locus, and results in a condition of hemizygosity The gene (or genes) present in the DNA sequence homologous to the deleted chromosome segment will thus be present in single 'dose' in the affected cell, and hence the hemizygotic state (*Figure 1*).

So far, at least 15 neoplasms have been found to be often associated with an unique type of deletion, some of which are shown in *Table 2*. The best known examples are retinoblastoma and Wilm's tumour, which occur in both sporadic and hereditary forms[28] A genetic basis for retinoblastoma has been apparent for many years, even though only about 10 per cent of patients have a positive family history[29]. In patients with a family history of the disease, inheritance occurs in a simple autosomal dominant fashion Furthermore, in about 30 per cent of patients with a new mutation, the disease is transmitted to about 50 per cent of the offspring. In 1971, Knudson[30] suggested a provocative theory, that the disease is triggered by two hit-processes, two events affecting the genome of a cell and resulting in its malignancy. Recent studies have clarified the situation and basically confirmed the hypothesis advanced by Knudson: both alleles of the gene must be altered in order for the disease to develop. The first studies were based on cytogenetic analysis of cells from patients in whom retinoblastoma was associated with multiple malformations and mental retardation These patients were shown to have a deletion in the long arm of chromosome 13 (Reference 31). Further investigations showed that a deletion of the band at q14 of chromosome 13 (13q14) could be seen in retinoblastoma cells of patients without the malformation syndrome[32,33]. These and other observations have provided evidence that retinoblastoma results from the inheritance of a germinal mutation which does not, in itself, cause malignancy but predisposes to it, and that a second 'hit' is necessary to trigger malignancy According to the theory, an individual may inherit the predisposing abnormal gene (*rb*, first hit), but only when a second gene change, such as a deletion (second hit), occurs in a susceptible cell (e.g. retinal cell) will the cell become malignant.

The story with Wilm's tumour began with the recognition that cancer cells from patients with a tumour of the kidney, associated with aniridia, had a deletion of the short arm of chromosome 11 at band p13 (11p13)[34]. Abnormality at this site is now considered to be the first event in the aetiology of Wilm's tumour and, as in retinoblastoma, the second event confers either hemizygosity for Wilm's gene (as a result of a deletion) or homozygosity for the abnormal gene (e.g by mitotic recombination) (*Figure 1*).

The body of evidence assembled so far from the study of these two tumours has led to the hypothesis that they originate because one normal suppressor or regulatory gene is lost in the course of the second hit, leaving only the abnormal gene to trigger malignancy. Most recently, Whyte *et al.*[35] have isolated a $10{\cdot}5 \times 10^4$ protein as a product of the retinoblastoma gene. They postulate that this protein might be acting as an 'antioncogene' whose presence initiates suppression of cell division. To support this idea they have observed that a DNA tumour virus, adenovirus E1A, produces a protein which binds the normal $10{\cdot}5 \times 10^4$ protein gene product. Furthermore they speculate that the tumour-inducing properties of this virus lie in its ability to turn off normal cellular suppression by binding the host cell's normal suppressor protein. This idea is supported by the finding that a deletion in the DNA of the tumour virus in the gene which produces the binding protein destroys the tumour-inducing properties of the virus[35,36]. Using probes which identify polymorphic DNA sequences (restriction fragment length polymorphisms) linked to the tumour loci, two other embryonal carcinomas—rhabdomyosarcoma and hepatoblastoma—have

Table 2 *Some deletions detected in human cancer cells*

Tumour	Chromosomal abnormality	Reference*
Retinoblastoma	Chromosome 13 (13q14)	23
Wilm's tumour	Chromosome 11 (11p13)	23
Lung cancer (small cell type)	Chromosome 3 (3p21)	23
Colon cancer (familial adenomatous type)	Chromosome 5 (5q21 or 5q22)	24
Breast cancer	Chromosome 11 (short arm)	25
Renal carcinoma	Chromosome 3 (3p11.2 or 3p13)	26
Osteosarcoma	Chromosome 13 (13q14)	27
Neuroblastoma	Chromosome 1 (1p31)	23

* Reference to reviews and recent papers

been shown to be due to genetic changes which result in hemizygosity or homozygosity for an abnormal gene[37].

During the last 2 years, other tumours have been found to be associated with unique types of chromosome deletions, which could only be detected using restriction fragment length polymorphisms. In the absence of any knowledge of the gene responsible for a specific tumour, the polymorphism of DNA sequences closely linked to the cancer gene can be exploited to establish the presence or absence of a deletion (see *Figure 1*). This strategy has been employed, for example, to investigate oncogenesis in patients with cancer of the lung, the colon or the breast.

A small deletion of chromosome 3 is the most constant finding in cancer of the lung tissue. Using a large panel of lung cancer cell lines representing all the different histological types (squamous or epidermoid carcinoma, adenocarcinoma, small cell carcinoma, and combined type) Minna *et al.*[38] were able to identify a gene on the short arm of chromosome 3 which may predispose to cancer of the lung. According to this hypothesis, individuals at risk would be heterozygous for this recessive gene, carrying one mutant and one copy of a normal functional gene in each cell. In these individuals environmental factors, in particular cigarette smoke, may produce somatic changes—such as a deletion or a mutation of the normal gene—in a lung cell, thus unmasking the abnormal gene. Loss of the normal gene is suspected to deregulate the expression of a proto-oncogene of the c-*myc* family or other gene controlling the synthesis of growth factor.

Deletion of a DNA sequence at the chromosomal region 3p21 in patients with lung cancer has been confirmed in a recent study[39]. In fact, using a molecular genetic approach, consistent deletion of the chromosome region 3p21 was observed not only in small cell lung cancer but also in all major types of lung cancer investigated. Part of the analysis was carried out using cell lines obtained from the tumours. A series of 16 biopsies from squamous cell carcinoma and 14 adenocarcinomas was also investigated. In several patients where heterozygosity for the selected DNA marker was detected using peripheral blood leucocytes, the tumour cells showed hemizygosity, thus revealing loss of the DNA region (3p21, locus DNF 15 5e). This confirms that somatic mutation of a gene at 3p21 is involved in the development of cancer of the lung.

In the case of cancer of the colon, a single patient was initially observed with a deletion of part of the long arm of chromosome 5 (5q), who, in addition to various developmental disorders, had multiple adenomatous polyps of the large bowel[40]. Linkage analysis of patients with cancer of the colon and their relatives, using a series of genetic probes defining polymorphic DNA segments (restriction fragment length polymorphisms) in the long arm of chromosome 5, has recently confirmed that indeed the familial adenocarcinomatous polyposis gene maps to chromosome 5 (5q21 or 22)[24,41]. In a parallel study, loss of heterozygosity in this DNA region was demonstrated in about 20 per cent of patients with spontaneous colon cancer[42] Thus inherited and sporadic forms of cancer of the colon both result from mutation in the same gene, in analogy with the hypothesis advanced by Knudson[30] for retinoblastoma and Wilm's tumour[43]. Both these mutations act in a recessive form and both normal allelic genes must be altered for cancer to develop. In the sporadic cases both events occur somatically, whereas in the familial cases susceptibility is inherited through germ-line mutation and cancer develops after a somatic change in the homologous allele (*Figure 1*)

Somatic loss of heterozygosity for genes on chromosome 11 has also been observed in some patients with cancer of the breast[25]. Deletions of various DNA sequences of the short arm of chromosome 11 were observed in about 20 per cent of breast cancer tissue biopsies obtained from 56 patients tested, and a significant association was noticed with tumours that lacked oestrogen and progesterone receptors.

Renal carcinoma, the most frequent form of malignancy of the human kidney, usually occurs during the sixth and seventh decades of life. Most tumours are sporadic, but hereditary forms have been described and are characterized by an early onset and bilateral localization. Cytogenetic studies have indicated that the short arm of chromosome 3 (3p) is the most frequent site of non-random abnormalities in both hereditary and sporadic types[26,44]. A recent investigation by Kovacs *et al.*[45] has confirmed the high incidence of anomaly of chromosome 3, distal to band 3p11.2 or 3p13 manifested as a deletion. Restriction fragment length polymorphism analysis in patients with sporadic cancer of the kidney has shown loss of heterozygosity for one marker (D1S1) in 76 per cent of cases and for another marker (D3S2) in another 18 per cent of patients.

Conclusions

At present, the prevailing working hypothesis about oncogenes is that they are involved in the process of tumorigenesis as a result of a mutation which may directly affect their function as growth factors or may activate a growth factor gene. This would induce a state of autocrine stimulation of the cell and consequently its abnormal proliferation. On the other hand a mutation of a specific receptor for a growth factor may induce autostimulation and consequent prolonged cell division. Another possibility is that the cell may be stimulated by the abnormal functional behaviour of a cell receptor via a mediator released in the cytoplasm by a cell receptor for a growth factor.

Finally, as already mentioned, the concept of the anti-oncogene and its role in tumorigenesis should be kept in mind[35,46]. The gene product of the antioncogene may act normally to suppress cell division. When this gene or its gene product is inactivated, uncontrolled proliferation occurs.

Probably the process of tumorigenesis is more complex than this, and the main question to answer is: why should a deletion such as 13q14 in an embryonal retinal cell result in a retinoblastoma while the same deletion in another type of cell does not induce malignancy? One possible explanation is that random deletions occur frequently in many cells and in most cases they may be either tolerated or lethal, but in some cells the same deletion induces abnormal growth and thus cancer. Further investigation should elucidate the role that genetic predisposition to a certain type of cancer, together with environmental agents, may have in triggering the disease and whether prevention can be achieved in relatives of the patient. It has been suggested, for example, that cancer of the lung is due to the presence of an abnormal recessive gene on chromosome 3 and that the deletion observed in this type of tumour (3p21) involving the normal gene may be induced by tobacco smoking If this hypothesis turns out to be correct, patients at risk could be identified and preventive measures implemented. It is at this level of prevention that the close collaboration among oncologists, geneticists and surgeons is essential.

Acknowledgements

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Anastomotic suture materials and implantation metastasis: an experimental study

J. R. McGregor,
D. J. Galloway,
P. McCulloch and
W. D. George

University Department of Surgery, Western Infirmary, Glasgow G11 6NT, UK

Correspondence to:
Dr J R. McGregor

Suture implantation of viable exfoliated malignant cells may be responsible for local recurrence (implantation metastasis) of colorectal cancer. In this study, four anastomotic materials (braided polyamide, braided polyglycolic acid, monofilament polypropylene and monofilament stainless steel) were compared with respect to their ability to entrap and transfer free Mtln3 carcinoma cells from the colonic lumen of a rat. The braided materials transferred greater numbers of cells than did the monofilament sutures ($P<0{\cdot}001$)*, but significant differences were also observed between polyglycolic acid and polyamide* ($P<0{\cdot}001$) *and between polypropylene and stainless steel* ($P<0{\cdot}05$)*. Secondly, the firm adherence of tumour cells to the suture materials was assessed by an* in vitro *technique. The Mtln3 cells were found to adhere in significantly greater quantities to the braided sutures than to the monofilaments* ($P<0{\cdot}001$) *and this was supported by* in vivo *tumour growth studies. These findings may have implications for colorectal cancer surgery in man.*

Keywords: Suture implantation, exfoliated malignant cells, local recurrence, colorectal cancer, implantation metastasis, braided sutures, monofilament sutures, adherence

Local recurrence is a major cause of morbidity and mortality following surgery for large bowel cancer. The reported incidence is variable[1–4], but a recent multicentre prospective study estimated the local recurrence rate to be approximately 14 per cent of patients who undergo ostensibly curative resection for colorectal cancer in the UK[5]. Around 80 per cent of cases present within the first 2 years of operation[3,6], and for the majority of patients no further 'curative' surgical intervention is feasible[7,8].

There is considerable clinical[9–11] and experimental evidence[12] to suggest that local recurrence may result from the surgical implantation of viable exfoliated malignant cells. Experimental studies have suggested that suture materials used to construct the anastomosis may have a part to play in this mechanism, a process frequently termed implantation metastasis. It has been shown that sutures are able to transfer malignant cells either from a solid tumour mass or from a cell suspension[13] in sufficient numbers to result in tumour growth in recipient animals, and that certain sutures can potentiate tumour growth when implanted into experimental animals with an inoculum of tumour cells[14]. Recent work has demonstrated that tumour cells differentially adhere to suture materials in a manner akin to bacterial adhesion[15].

This study was designed to assess the potential role of four anastomotic suture materials in implantation metastasis Two separate experiments were performed. The aim of the first was to compare the various materials with respect to their *in vivo* entrapment of free intraluminal tumour cells and the resultant transfer of these cells from the colonic lumen. The second experiment compared the extent of tumour cell adhesion to the same four materials, measured by an *in vitro* adhesion assay. *In vivo* tumour growth studies were also performed.

Materials and methods

Tumour cell line

The tumour used was the Mtln3 clone of the rat mammary adenocarcinoma 13762NF, cells of which were donated to the department by the originators of the clone, Drs Neri and Nicolson of the M D Anderson Hospital and Tumor Institute, Houston, Texas, USA The cells were cultured in either 75 cm^2 or 160 cm^2 tissue culture flasks (Nunc/Intermed, Kamstrup, Denmark) in medium consisting of equal parts of Hams's F10 and Dulbecco's modified Eagle's medium (F10/DMEM) with 10 per cent added fetal calf serum (FCS). Cultures were maintained at 37°C in an atmosphere of 2 per cent carbon dioxide in air and moved a maximum of six times between thawing and experimental use to minimize problems of phenotypic drift[16].

Suture materials

Four suture materials were tested. These comprised braided polyamide (Nurolon®, Ethicon Ltd., Edinburgh, UK), braided polyglycolic acid (Dexon Plus®, Davis and Geck, Gosport, UK), monofilament polypropylene (Prolene®, Ethicon Ltd.) and monofilament stainless steel (Ethicon Ltd), the latter being identical in composition to the material used in the manufacture of surgical staples Sutures of 5/0 gauge were used throughout.

Preparation of labelled cell suspension

A suspension of 10^7 Mtln3 cells per millilitre of F10/DMEM was prepared from near-confluent cultures. Cells were removed from the tissue culture flasks by treatment with Ca^{2+} and Mg^{2+} free phosphate buffered saline (PBS) followed by incubation for 10 min in 0 2 per cent trypsin (Gibco Ltd., Paisley, UK) at 37°C. An excess of F10/DMEM + 10 per cent FCS was then added to the culture flasks to neutralize trypsin activity, after which the cells were washed three times in this medium by centrifugation at 300*g* for 5 min and resuspension of the cell pellet Following the final resuspension, the cells were counted and the dilution adjusted Cell viability was ascertained by Trypan Blue exclusion and suspensions with over 95 per cent viabiltiy were obtained

Cells were then radiolabelled with ^{51}Cr which was obtained as sodium chromate ($Na_2{}^{51}CrO_4$) in minimal volume. A dose of 10 MBq of radiochromium was used per 10^7 tumour cells in a total volume of 4 ml. Labelling was carried out by incubation of the cell/^{51}Cr suspension for 90 min in a thermostatically regulated water-bath at 37°C with constant agitation Once incubation was complete, the tumour cells were washed four times in fresh RPMI 1640 + 10 per cent FCS medium (Flow Laboratories Ltd , Rickmansworth, UK) before counting of cell numbers and further assessment of viability. Finally the dilution was adjusted to produce a suspension of 10^7 viable labelled cells per millilitre of culture medium.

The in vivo *entrapment and transfer of tumour cells by sutures*

Twelve-week-old fasted male Fischer F344 rats were used throughout. Laparotomy was performed through a long midline incision and all residual faecal material was milked out of the caecum into the distal

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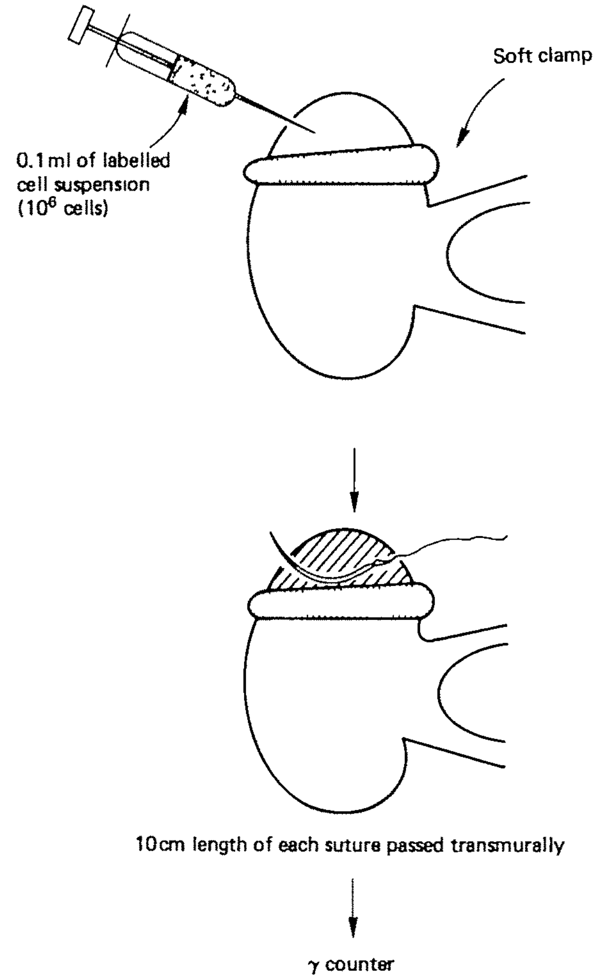
Soft clamp
0.1 ml of labelled cell suspension (10^6 cells)
10cm length of each suture passed transmurally
γ counter

Figure 1 In vivo *entrapment and transfer of Mtln3 cells in the wall of rat caecum*

colon Animals were then killed and immediately transferred to the radioisotope laboratory. An occlusive clamp was placed to isolate the upper caecal pole, into the lumen of which 0·1 ml of the radiolabelled tumour cell suspension was injected via a 24 gauge needle (*Figure 1*) A single 10-cm length of each of the four suture materials in turn was passed transmurally through this isolated, tumour-cell-containing segment, and the sutures were immediately transferred to the γ counter for measurement of radioactivity. Animals were used in groups of four or eight and the order in which the four types of suture were passed through the caecum was predetermined by a Latin square distribution which ensured that each suture was placed in each rank order once in every group of four animals (or twice in every group of eight)

The entire experiment was performed four times. twice with four animals and twice with eight For each assay the activity of a standard radiolabelled tumour cell suspension (10^6 labelled cells) was measured to allow calculation of the number of tumour cells adherent to the sutures. Background radioactive count was also measured and corrected for in the calculations.

The in vitro *adhesion of tumour cells to sutures*

Aliquots of 10^7 labelled tumour cells, each in 4 ml of F10/DMEM/FCS medium, were placed in four centrifuge tubes, one corresponding to each of the suture materials under test. Each tube received three separate 10-cm lengths of the appropriate suture material and the suspensions were incubated for 90 min at 37°C in the water-bath with constant agitation Each length of suture was then carefully removed with fine forceps and washed in PBS to remove any non-adherent cells This step was standardized by placing a beaker of PBS on a magnetic stirrer to produce a moving stream of PBS in which each length of suture was held for 15 s at a standard stirring speed and distance from the centre. Thereafter radioactivity was measured as before. This experiment was repeated four times in total and, as for the previous study, the radioactivity of standard labelled cell suspensions were used to calculate the number of cells that adhered

Controls

The above experiments were repeated using a cell-free solution of $Na_2{}^{51}CrO_4$ in culture medium instead of the radiolabelled tumour cell suspension. The purpose of this was to determine if any difference observed between the various suture materials reflected a difference in the number of tumour cells involved or whether it simply represented the attachment of non-cell bound chromium to the sutures

In vivo *tumour growth studies*

In the previous *in vivo* experiment the radioactivity levels of the sutures were measured within a very short period from the preparation of the cell suspension and so cell viability was assumed throughout. However, in the *in vitro* study, cell viability could not be assumed after the 90-min period of incubation To demonstrate tumour cell viability, lengths of each suture material were inserted transmurally into the caecum of 12-week-old male F344 rats after exposure to Mtln3 cells as described in the *in vitro* experiment The number of animals developing caecal tumours was recorded for each type of suture

Eight animals were used for each of the four anastomotic materials. Under ether anaesthesia, laparotomy was performed through a midline incision and five interrupted transmural sutures were placed in the upper caecal pole. All knots were tied loosely on the serosal surface and the abdominal incision was closed with continuous silk suture. Animals were killed on the 21st postoperative day and a full autopsy was performed The procedure was later repeated with a further 24 animals, six per suture material, and on this occasion groups of rats were only killed when the animals were visibly unwell or when two or more members of the group had died

Statistical methods

For the *in vivo* and *in vitro* experiments an overall statistical assessment was made using the Kruskal–Wallis test. Comparisons between individual suture materials were made using the Mann–Whitney U test Results for the *in vivo* tumour growth studies were compared using Fisher's exact test

Results

Tumour cell entrapment and transfer in vivo

Both the braided suture materials and, in particular, polyglycolic acid transferred significantly greater numbers of tumour cells from the caecal lumen than did either monofilament stainless steel or monofilament polypropylene ($P<0{\cdot}001$; Mann–Whitney U test) (*Table 1*). Polyglycolic acid transferred a significantly greater number of tumour cells than polyamide ($P<0{\cdot}001$). The number of cells transferred by polypropylene was significantly greater than the number transferred by stainless steel ($P<0{\cdot}05$). The median numbers of Mtln3 cells transferred per suture for each material are illustrated diagrammatically in *Figure 2.*

Tumour cells adherence in vitro

The Mtln3 tumour cells firmly adhered in significantly greater numbers to the two braided suture cells than they did to either of

Table 1 *The* in vivo *entrapment and transfer of Mtln3 cells by suture materials*

Suture material	Median number of cells transferred *in vivo*	Range of values
1. Polyamide	4226	1348–15175
2. Polyglycolic acid	13987	4671–30616
3. Stainless steel	1197	59– 3434
4. Polypropylene	545	141– 3371
Comparison*	**95% confidence interval**	***P* value**
1 *versus* 2	5659–13305	<0·001
1 *versus* 3	2519– 4560	<0·001
1 *versus* 4	1900– 4053	<0·001
2 *versus* 3	9924–17661	<0·001
2 *versus* 4	9331–17088	<0·001
3 *versus* 4	45– 1011	<0·05

* Results of Mann–Whitney U tests

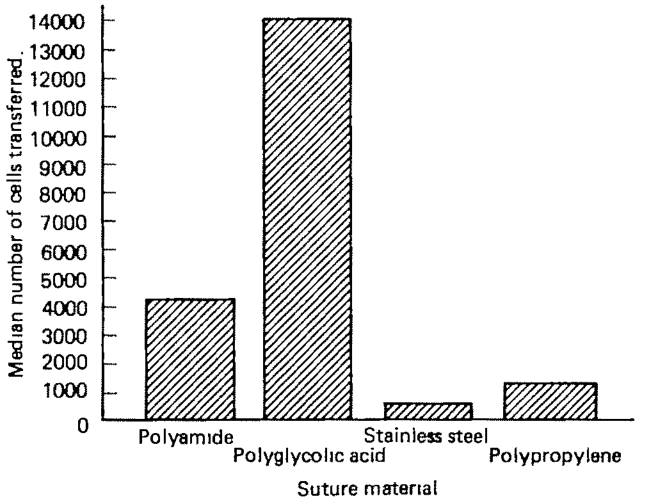

Figure 2 *The median number of Mtln3 carcinoma cells transferred* in vivo

Table 2 *The* in vitro *adherence of Mtln3 cells to suture materials*

Suture material	Median number of cells adhered *in vitro*	Range of values
1. Polyamide	2911	1003–10125
2. Polyglycolic acid	7082	2342–27095
3 Stainless steel	155	56– 662
4. Polypropylene	282	172– 861

Comparison*	95% confidence interval	*P* value
1 *versus* 2	265–11719	=0·05 (n.s)
1 *versus* 3	1433– 7172	<0·001
1 *versus* 4	1544– 7302	<0·001
2 *versus* 3	3691–14410	<0·001
2 *versus* 4	3646–14540	<0·001
3 *versus* 4	−27– 221	=0·07 (n s)

* Results of Mann–Whitney *U* tests; n.s., not significant

the monofilaments (*Table 2* and *Figure 3*). Despite the very wide range of values recorded these differences between the braids and monofilaments were highly significant statistically ($P < 0{\cdot}001$) However, in this experiment polyglycolic acid and polyamide could not be separated statistically nor could stainless steel and polypropylene.

Results using free ^{51}Cr

There were no significant differences between the various suture materials with respect to the measured radioactivity levels when either of the experiments was performed using the solution of free ^{51}Cr. The results are expressed in *Table 3* as medians and ranges.

Animal controls

Of the first group of 32 animals killed on the 21st postoperative day, 19 had macroscopic tumours of the upper caecal pole. No histological abnormalities were seen in the 13 macroscopically normal animals apart from a variable acute inflammatory infiltrate. The distribution of the animals developing tumours according to the type of suture material was as listed in *Table 4*.

When the experiment was repeated with the group of 24 rats in which killing was delayed, only two animals (one with stainless steel suture, one with a polypropylene suture) were found to be tumour free at autopsy. The remainder all had macroscopic evidence of intra-abdominal tumour although the time from surgery until the animals were visibly unwell did appear to correlate with the type of suture material. Two of the animals with polyglycolic acid sutures died on day 26 and the group was therefore killed on that day. The group with polyamide sutures was also sick by this time and was similarly killed. The group with stainless steel sutures remained healthy until day 33 when two of the rats were noted to be unwell whereas the group with polypropylene sutures did not reach this stage until day 36.

Discussion

In recent years there has been little change in the long-term prognosis following 'curative' resection of colorectal cancer. The overall 5-year survival of such patients treated in specialist institutions remains around 50–60 per cent[2,17] and the incidence of local recurrence is a major factor limiting improvements in this figure. As this clearly represents a local failure of surgical management, the relationship between surgical technique and local recurrence merits further investigation, particularly in the light of some recent reports suggesting a possible association

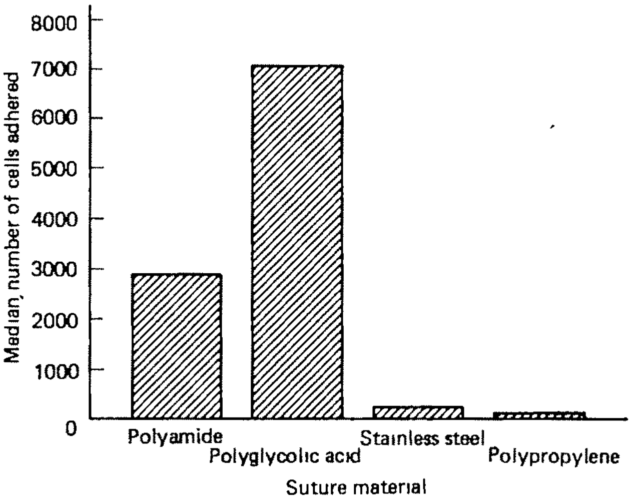

Figure 3 *The median number of Mtln3 carcinoma cells adhered* in vitro

Table 3 *Radioactivity counts of sutures using free* $Na_2{}^{51}CrO_4$ *solution*

Suture material	*In vivo* study	*In vitro* study
Polyamide	223 (171–365)	197 (136–504)
Polyglycolic acid	403 (179–490)	284 (131–739)
Stainless steel	399 (144–698)	144 (97–243)
Polypropylene	220 (142–407)	159 (114–337)

Values are median (range) counts/min

Table 4 In vivo *tumour growth studies animals with caecal tumours at 21 days*

Suture material	No of animals	No. with caecal tumours
Polyamide	8	7
Polyglycolic acid	8	8
Stainless steel	8	3
Polypropylene	8	1

Comparison*	*P* value
Polyamide *versus* polypropylene	<0·01
Polyamide *versus* stainless steel	(n.s)
Polyglycolic acid *versus* stainless steel	<0·05
Polyglycolic acid *versus* polypropylene	<0·001

* Results of Fischer's exact test, n.s., not significant

between stapled colorectal anastomoses and an enhanced risk of local recurrence[18,19].

In 1885, Gerster proposed that the mechanical dissemination of tumour cells at operation might be responsible for local recurrence[20]. Support for this hypothesis came when McGrew *et al* demonstrated malignant cells in Papanicolaou smears taken from both the proximal and distal resection margins of colonic cancer resection specimens[21]. Rygick *et al.* reported similar findings in smears taken from surgical instruments and from the surgeon's gloves[22] Although the viability of these exfoliated cells, and hence their ability to give rise to recurrent tumour, was subsequently questioned by Rosenberg *et al.*[23], it has recently been demonstrated that viable tumour cells are present in large numbers in the colonic lumen of patients with colorectal cancer[10].

Free tumour cells are incapable of implanting on normal colonic mucosa but they will readily grow on serosal and peritoneal surfaces[24]. While the divided bowel ends at an anastomosis, with their exposed serosa and raw muscle edges, obviously present a fertile field for tumour cell implantation, the suture material used to construct the anastomosis may also have a part to play The implantation of tumour cells by suture materials has been described in animal models[12,13] and it has been demonstrated that the use of iodized sutures effectively decreases the incidence of tumour development in such experimental studies[25,26]. Suture materials may be further implicated in implantation metastasis in that they may act as a nidus for the adherence of tumour cells once they have been implanted into the colonic wall[15].

In this study we have shown that, of the anastomotic materials tested, the two braided sutures were able to entrap and transfer significantly greater numbers of free intraluminal tumour cells *in vivo* than were either of the monofilament materials ($P<0{\cdot}001$). The results from the *in vitro* study suggest that the braided sutures have a greater propensity to act as a nidus for implanted malignant cells since the tumour cells adhered in significantly greater numbers to them than they did to the monofilaments. The animal studies served to illustrate the highly malignant nature of the tumour cell line used in these experiments and the persistent viability of Mtln3 cells incubated *in vitro* with ^{51}Cr for 90 min. The differences recorded in tumour growth correlated precisely with the rank order in which the *in vitro* study placed the adhesion of tumour cells to each suture material.

We conclude that the choice of anastomotic suture material may have an important influence on the risk of implantation metastasis. Should this mechanism apply to colorectal cancer surgery in man, then our results would suggest that monofilament suture materials may be associated with a lesser risk of local recurrence than are braided materials. However, the significant differences between polyamide and polyglycolic acid and between polypropylene and stainless steel with respect to the *in vivo* entrapment and transfer of tumour cells suggest that the composition of a suture material is important in addition to its physical characteristics. Further investigation of a variety of commonly used anastomotic suture materials is therefore warranted as part of the continuing search for ways of reducing the incidence of local recurrence after apparently curative surgery for large bowel cancer

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Recurrence after strictureplasty or resection for Crohn's disease

J. Sayfan, D. A. L. Wilson*, A. Allan, H. Andrews and J. Alexander-Williams

*The General Hospital, Birmingham and *Applied Statistics Group, Aston University, UK*

Correspondence to:
Professor J. Alexander-Williams,
The General Hospital, Steelhouse
Lane, Birmingham B4 6NH, UK

This study attempts to define whether there is an increased need for reoperation in patients with small bowel Crohn's disease treated by strictureplasty compared with those treated by small bowel resection. Previous studies of the rate of reoperation for small bowel Crohn's disease do not distinguish between reoperation performed because of a lesion at the original operation site and that undertaken because of a lesion at a distant site. This study analyses the need for reoperation only at the original site of operation and measures operation-free intervals. The site specific operation-free intervals in 41 patients with small bowel Crohn's disease treated by strictureplasty were not significantly different from the similar intervals in 41 patients treated by a small bowel resection.

Keywords: Crohn's disease, strictureplasty and resection for Crohn's disease, reoperation for Crohn's disease

Over the past decade, strictureplasty has become a useful technique in the surgical management of strictures in small bowel Crohn's disease[1]. Although an intestinal resection is the operation of choice for the common presentation of Crohn's disease confined to the ileocaecal region[2–4], strictureplasty is a convenient, simple and safe technique when the distribution of the disease makes multiple resections impractical, as in patients with multiple short areas of small bowel Crohn's disease.

Resection involves removal of the macroscopically diseased bowel whereas with strictureplasty the diseased bowel remains. Therefore it is possible that recrudescence of symptomatic Crohn's disease at the site of operation might occur earlier following strictureplasty than following resection. Many studies record the incidence of reoperation in patients who have previously undergone surgery for small bowel Crohn's disease[2–8] but they do not differentiate between recrudescence of disease at the original site of operation and recrudescence at sites distant from the site of previous surgery.

To assess the efficacy of strictureplasty in the management of individual strictures it is necessary to consider the need for reoperation at the site of the original stenosis rather than that carried out because of recrudescence of disease at other sites.

Patients and methods

A retrospective analysis was made of the case records of two groups of patients that had undergone surgery at the General Hospital, Birmingham for Crohn's disease of the small bowel.

Group A consisted of 41 patients in whom the disease had been treated by resection only. Group B consisted of another 41 patients in whom the disease had been treated at least once by strictureplasty; 36 patients in this group had also undergone at least one bowel resection for Crohn's disease. The two groups of patients were well matched for age, sex and the length of follow-up (*Table 1*). When combined, the two groups comprised 82 patients who had undergone a total of 174 small bowel resections and 129 strictureplasties (*Table 2*).

Our analysis was concerned with individual sites of disease within patients and, in particular, with the times between procedures at each site, which we refer to as 'reoperation-free intervals'. We studied 44 separate sites in the 41 patients of group A and 136 sites in the 41 patients of group B. For patients who had undergone surgery at more than one site, there was clear documentation which enabled us to distinguish reoperation-free intervals for each site separately.

Statistical analyses

Statistical comparisons between rates of reoperation following resections and strictureplasties are limited by the fact that strictureplasty has only been used widely in our hospital since 1981, whereas the records for resections go back for more than 40 years. Many patients treated by strictureplasty are still under 'open follow-up' (no reoperation yet required) and so we have only censored estimates of the intervals (i.e. lower limits on the final values of these intervals). In contrast, we have more completed intervals for the time to reoperation following resection and have longer periods of open follow-up. As a result, we are cautious about comparisons between the two procedures beyond the first few years after each operation. Our sample included 26 patients who had undergone at least two resections at the same site: eight of each sex from group A and five of each sex from group B. The coefficient of correlation between their first and second reoperation-free intervals was only 0·25 and a Wilcoxon signed rank test showed that there was no significant difference between the mean first and second intervals ($P = 0·052$), so we subsequently treated all intervals as independent and homogeneous.

The apparent multiplicity of sites amongst the patients who had undergone resection (41 of group A and 36 of group B) is caused almost entirely by these patients having received successive resections at a single site. Only two patients (one man and one woman, both in group B) recorded completed post-resection intervals at a second site, seven others recorded censored intervals at only one additional site, and one recorded censored intervals at two additional sites.

Because most of the strictureplasty sites are still under open follow-up, we have little information about the joint distribution of intervals after this procedure at different sites in the same patient. However, we see no reason to suppose that the correlation would be greater than that between successive intervals at the same site after resection.

The percentage of sites free of reoperation as a function of time in months was calculated by the Kaplan–Meier technique[9], which is especially suitable for relatively small samples and takes account of censoring (patients still under open follow-up). This technique was used to prepare *Figures 1* and *2*.

Table 1 *Details of 82 patients who had undergone operation for Crohn's disease of the small bowel*

Group	Mean age (years)	No. of patients (F:M)	Mean follow-up from first operation (years)
Group A			
Resection only ($n = 41$)	45 (25–85)	26·15	17·4 (1–39)
Group B			
Strictureplasty* ($n = 41$)	44 (20–76)	25:16	15·2 (1–45)

Ranges are given in parentheses, * 36 patients in this group had also undergone at least one bowel resection for Crohn's disease

Table 2 *Procedures carried out in 82 patients who had undergone surgery for Crohn's disease of the small bowel*

Procedures	Group A ($n = 41$)	Group B ($n = 41$)	Total
Strictureplasties	—	129	129
Resections	93	81	174

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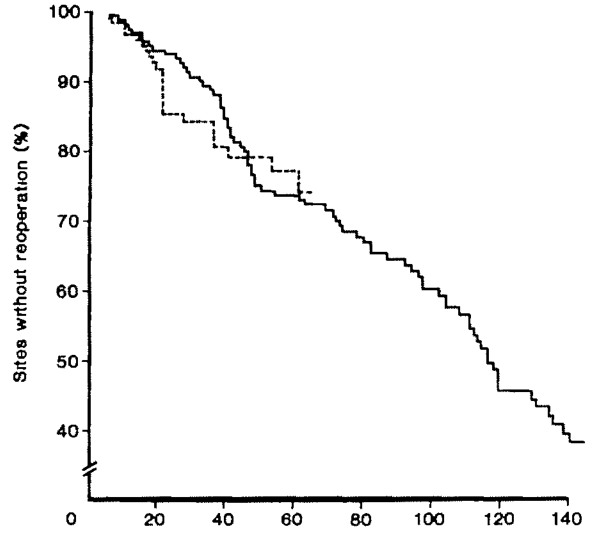
The log rank test[10] was used to check for significant differences between the Kaplan–Meier estimates for resections in groups A and B which are shown in *Figure 2* Because of the discrepancy in the lengths of follow-up, this test was not appropriate for comparing resections with strictureplasties (*Figure 1*) However, approximate standard errors for each curve were calculated by the method of Peto *et al* [10] (*Table 3*) and these were used for a rough check on differences between the curves



NO. OF SITES AT RISK								
Resections	173	153	126	103	87	68	44	30
Str. plasties	129	110	51	26	6	0	0	0

Figure 1 *Percentages of sites without reoperation* ——, *resection (groups A and B combined),* – – –, *strictureplasty (group B) (Kaplan–Meier estimates) The number of sites at risk are shown*

Sharp falls in the Kaplan–Meier curves indicate periods of increased risk of reoperation. This is best measured by the hazard rate[11] which represents the percentage of sites that remain unstrictured for the time to which the rate refers, then require reoperation shortly afterwards To obtain estimates of hazard rates in *Figures 3* and *4* we used the life table method[11] with 10-month intervals. Standard errors of these estimates are given in *Table 4*

Results

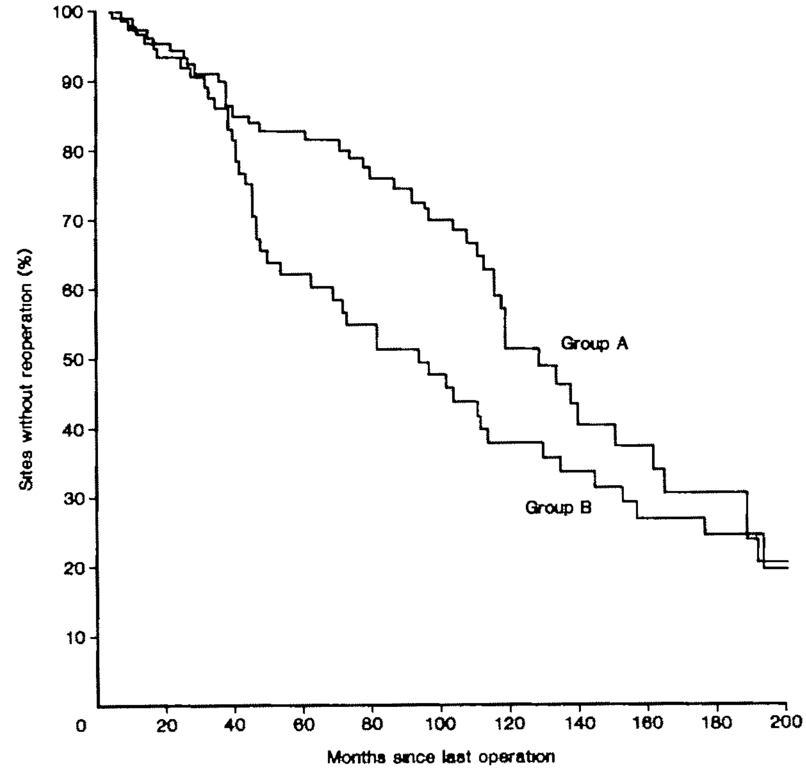
For the 60 months over which comparisons can be made, the Kaplan–Meier estimates indicate that there is no significant difference between the percentages of sites without reoperation after resection and the corresponding percentages after strictureplasty. The visual impression of *Figure 1* is reinforced by comparing the standard errors in *Table 3*, where it can be seen that the one-standard-error bands on either side of each curve always overlap.

The corresponding hazard rates are shown in *Figure 3*, where the resections exhibit two marked peaks, an early one (at about 40 months) and a late one (at about 110 months). Between these peaks, the hazard rate hovers around 0·5 per cent per month, i.e.

Table 3 *Kaplan–Meier estimates of percentages of sites without reoperation*

	Procedures	
Months	Resections (groups A and B)	Strictureplasty (group B)
20	94·6 (±1·8)	91·9 (±2·5)
40	83·5 (±3·0)	79·1 (±5·1)
60	73·9 (±3·7)	74·3 (±7·4)

Values are mean percentages with standard errors in parentheses



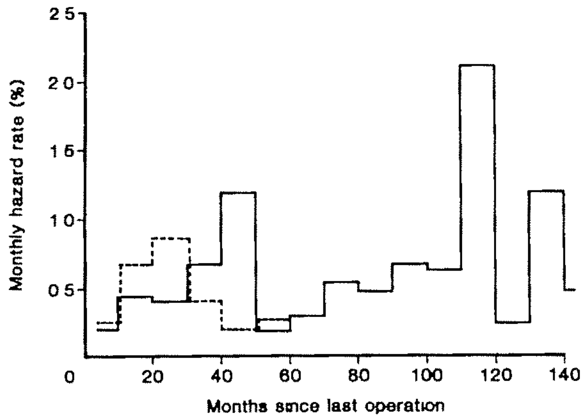
SITES AT RISK											
Group A	93	85	73	68	56	43	25	15	11	9	6
Group B	80	68	53	35	31	25	19	15	12	10	8

Figure 2 *Percentages of sites without reoperation group A, resections only, group B, strictureplasties with or without previous resections (Kaplan–Meier estimates) The number of sites at risk are shown*

6 per cent per annum. *Table 4* shows that these peaks clearly lie outside the one-standard-error limits of the other hazard rates. As the standard errors are only approximate, we also carried out a further check to find whether the underlying hazard rate for all resections was constant from 4 to 150 months.

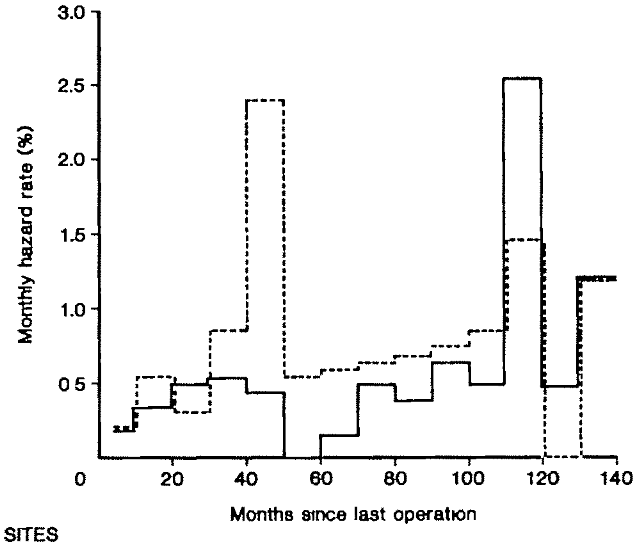
Considering all complete and randomly censored observations up to 150 months and the number of survivors at 150 months, we found that the maximum likelihood estimate of such a constant rate would be 0·57 per cent per month. A likelihood ratio test using the numbers of complete and censored observations in each of the 15 intervals then showed that our data were not compatible with this constant hazard rate hypothesis ($\chi^2 = 33{\cdot}5$, d.f. between 14 and 15, $P < 0{\cdot}005$). The choice of a 150-month horizon is arbitrary, but this test confirms our belief in the reality of the peaks. There is also a suggestion of a peak at about 20 months on the graph of the strictureplasty hazard rate (*Figure 4*). This may represent a forward shift in the restricturing time represented by the 40-month peak for resections (*Figure 3*). The minimum observed interval between operations was 5 months for both procedures. To allow for the possibility of a slightly shorter interval, the hazard rates for the first 10 months were calculated on the assumption that the minimum possible interval was 4 months (*Figures 3* and *4*).

Before combining the results for all the resections to obtain the Kaplan–Meier curve in *Figure 1*, we had analysed separately those performed alone (group A) as well as those performed in combination with strictureplasty (group B) as shown in *Figure 2*. Despite the visual difference between the two curves the log rank test showed that, overall, there is no significant



NO OF SITES AT RISK								
Resections	173	153	126	103	87	68	44	30
Str. plasties	129	110	51	26	6	0	0	0

Figure 3 *Monthly reoperation hazard rates* ——, *resection (groups A and B combined),* – – –, *strictureplasty (group B) (life table estimates) The number of sites at risk are shown*



SITES AT RISK								
Group A	93	85	73	68	56	43	25	15
Group B	80	68	53	36	31	25	19	15

Figure 4 *Monthly reoperation hazard rates* ——, *resections (group A),* – – –, *strictureplasties in patients with or without previous resections (group B) (life table estimates). The number of sites at risk are shown*

Table 4 *Monthly hazard rates with approximate standard errors calculated by the method of Peto* et al.[10]

	Procedures			
	Resection			Strictureplasty
Months	Group A	Group B	Groups A and B	Group B
4	0·18 (±0·18)	0·21 (±0·21)	0·20 (±0·14)	0·26 (±0·18)
10	0·34 (±0·19)	0·55 (±0·27)	0·44 (±0·16)	0·68 (±0·23)
20	0·49 (±0·24)	0·31 (±0·22)	0·41 (±0·16)	0·87 (±0·28)
30	0·53 (±0·26)	0·86 (±0·40)	0·67 (±0·22)	0·41 (±0·23)
40	0·43 (±0·24)	2·39 (±0·63)	1·20 (±0·30)	0·20 (±0·19)
50	0·00 (±0·00)	0·54 (±0·37)	0·19 (±0·13)	0·27 (±0·27)
60	0·15 (±0·15)	0·59 (±0·41)	0·30 (±0·17)	
70	0·50 (±0·28)	0·63 (±0·43)	0·55 (±0·25)	
80	0·37 (±0·26)	0·68 (±0·46)	0·48 (±0·23)	
90	0·64 (±0·36)	0·75 (±0·51)	0·68 (±0·29)	
100	0·49 (±0·34)	0·85 (±0·58)	0·63 (±0·31)	
110	2·54 (±0·78)	1·46 (±0·78)	2·12 (±0·57)	
120	0·47 (±0·46)	0·00 (±0·00)	0·25 (±0·25)	
130	1·21 (±0·80)	1·21 (±0·80)	1·21 (±0·57)	
140	0·71 (±0·68)	0·69 (±0·67)	0·70 (±0·48)	

Values are mean monthly hazard rates as percentages with the standard error in parentheses difference between them ($\chi^2=2.19$, $P=0.14$) However, this test is not specifically concerned with peaks in the hazard rates In *Figure 4* it can be seen that the reoperation hazard rate in patients having had resections alone and in those having resection combined with strictureplasty make different contributions to the early and late peaks. The early peak is made up almost entirely of contributions from the patients undergoing resections combined with strictureplasty (group B). The larger part of the later peak comes from those having resection alone (group A).

Discussion

In this study no significant difference was found in operation-free intervals following resections or strictureplasties for obstructive small bowel Crohn's disease. Statistically valid comparisons could be made for the first 60 months only, owing to the recent introduction of strictureplasty (*Figure 1*) Nevertheless, this finding seems to support the claim that remaining disease does not precipitate early recrudescence at the operated site[8,12].

Since 1971 several authors have presented 'circumstantial' evidence suggesting the possibility that two clinical forms of Crohn's disease might exist: an 'aggressive' form of the disease has a tendency to higher recurrence rates, more extensive involvement, and more abscess and fistula formation, while the other form is characterized by a more quiescent clinical course. This hypothesis was based on observations concerning the relationship between the duration of the disease before the initial operation and the subsequent reoperation rate Correlation between types of indications and recurrence rates has also been demonstrated and several studies have shown biphasic cumulative curves of recurrence (early and late reoperations)[5–8,13]. Our findings seem to support this view in that the reoperation rates following resections clearly show two peaks (*Figure 3*) at 40 and 110 months. When the hazard rates were calculated separately for each group (*Figure 4*), the peaks were still present. However, the interesting point that emerged was that the early peak was composed almost exclusively of contributions from resections in group B patients (strictureplasty, some with resection), whereas the major component of the late peak was from group A patients (resections only) This early peak of reoperation hazard rate in the group of patients who had more extensive and multifocal disease (as most of them required multiple strictureplasties and simultaneous resections) might represent the more aggressive form of disease However, identification of the two peaks on the hazard rate with separate forms of the disease must remain speculative until further data become available.

The minimal interval between reoperations was 5 months for both procedures. As the intervals refer to specific sites only, it is interesting to note that there might be a minimal 'restricturing time' which is similar regardless of whether the diseased segment is excised or left *in situ*.

In conclusion, strictureplasty appears to be an alternative to wide or multiple resections for multifocal stenotic small bowel Crohn's disease. It is indicated particularly in those patients in whom multiple short segments are involved and obstructive symptoms are present. Whether function of the preserved bowel is worthwhile, or whether this bowel carries an increased risk of malignancy (as appears to follow bypass procedures) remains unknown.

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Ten-year experience of strictureplasty for obstructive Crohn's disease

T. C. B. Dehn, M. G. W. Kettlewell, N. J. McC. Mortensen, the late E. C. G. Lee and D. P. Jewell

Departments of Surgery and Medicine, John Radcliffe Hospital, Oxford, UK
Correspondence to:
Mr T. C B Dehn, Department of Surgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

Strictureplasty is controversial in the management of obstructive Crohn's disease. Only a small proportion of patients undergoing surgery for obstructive Crohn's disease are suitable for strictureplasty. Lesions which are most amenable for this procedure are short, fibrous strictures. Over a 10-year period 24 patients have undergone 30 operations at which 86 strictureplasties were performed. The median follow-up has been 40 (range 4–112) months. No leaks or fistulae arose from the strictureplasties. The median weight gain 3 months postoperatively was +4·0 kg. Four patients subsequently required a further 13 strictureplasty procedures, between 12 and 36 (median 18) months after the initial operation; all but one of the previous strictureplasties were patent. Thirteen patients have been symptom free following surgery, four have required further medical therapy for recurrent Crohn's disease and three have sustained episodes of self-limiting intestinal colic. Strictureplasty is a safe and effective procedure in selected patients undergoing surgery for obstructive Crohn's disease.

Keywords: Crohn's disease, intestinal obstruction, minimal surgery, strictureplasty

Approximately one-third of patients with Crohn's disease will require repeated surgery for recurrent disease[1,2]. One of the risks of repeated or extensive resection is malnutrition due to the short bowel syndrome.

The concept of minimal surgery for Crohn's disease[3–5] has been gaining acceptance and, in particular, the operation of strictureplasty is being more widely used. The technical aspects of the operation are controversial as not only does overtly diseased intestine remain unresected, but also the anastomosis is made through macroscopically affected bowel. Sceptics have feared a high rate of both fistulae and early relapse of Crohn's disease following this surgery.

This paper reports this unit's 10-year experience.

Patients and methods

Between 1 January 1978 and 1 January 1988, 24 patients (10 men, 14 women, median age 33 years, range 17–45 years) underwent 30 strictureplasty operations Patients were reviewed in the outpatient department ($n = 19$), and those living abroad were contacted by letter ($n = 5$).

The criteria for patients with obstructive Crohn's disease to be selected for possible strictureplasty were the presence of symptoms unresponsive to medical therapy and intestinal strictures on small bowel enema. At laparotomy all sites of macroscopic Crohn's disease were inspected; the following factors were those which influenced the decision to undertake strictureplasty in preference to excision of the affected obstructed segment: (1) length of remaining intestine, (2) length of affected segment, (3) inflammatory activity of affected segment, and (4) proximity of other affected segments.

Results

Eighty-six strictureplasties were performed at 30 operations. The median follow-up is 40 (range 4–112) months.

Prior history of Crohn's disease

Crohn's disease had been diagnosed for a median 72 (range 0–240) months In nine patients this diagnosis had been present for >10 years. Seventeen patients had, before strictureplasty, undergone 36 operations for Crohn's disease (25 small bowel resections, six right hemicolectomy and terminal ileal resections, two proctocolectomies, two gastroenterostomies, one split ileostomy).

Preoperative details

Obstructive symptoms had been present for a median of 4 (range 1–240) weeks. Intestinal Crohn's disease strictures were identified preoperatively by small bowel enema in 26 of 30 instances (87 per cent). Barium enema demonstrated ileocolic anastomotic strictures in two cases, plain X-ray demonstrated intestinal obstruction in one case and one patient underwent emergency laparotomy. The following nutritional and disease activity indices were recorded preoperatively (figures are median and range): weight 51 (32–76) kg; Hb 11·3 (10–14·4) g/100 ml; albumin 34 (18–43) g/l; and erythrocyte sedimentation rate 24 (3–64) mm/h.

Operative details

All patients received 5 days of intravenous cephalosporin and metronidazole and all but one patient received perioperative steroid therapy. Strictures were identified in 22 operations by the passage at enterotomy of a 36 Fr plastic oesophageal tube (external diameter 12 mm) and in the remaining eight by perenterotomy pull-through of a 20 Fr Foley balloon catheter, inflated with 3 ml of saline giving a balloon diameter of 2 cm (Reference 6).

Eighty-six strictureplasties were performed: 80 were jejunoileal, four at the site of previous ileocolic anastomoses, one at the duodenal–jejunal junction and one at the site of a previous strictureplasty; 78 were closed in the manner of Heinecke-Mickulicz, and eight similar to that of Finney. Anastomosis was by continuous one-layer 3/0 Vicryl® (Ethicon Ltd., Edinburgh, UK) or two-layer continuous 3/0 chromic catgut. The median length of the strictureplasty was 3 (range 1–17) cm. The number of patients having single or multiple strictureplasties was as follows: one procedure in 15 patients, two procedures in five patients, three in three patients, four in three patients, six in two patients, seven in one patient, and 21 in one patient Simultaneous intestinal resections were undertaken in 15 patients (12 jejunal–ileal resections, three ileocaecal resections).

Early postoperative (0–30 days) results

There were no deaths, fistulae or wound infections related to the operative site. One patient developed an intra-abdominal abscess and subsequent duodenocutaneous fistula from a missed duodenojejunal fistula. Parenteral nutrition was given post-

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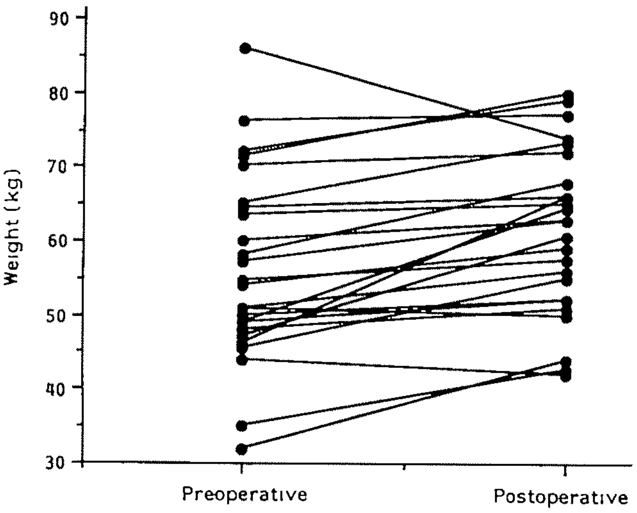

Figure 1 *Diagram illustrating preoperative and postoperative weights (kg) at 3 months recorded after 26 strictureplasty operations*

operatively to 23 of 30 (77 per cent) patients for a median of 7 (range 5–18) days. The median time between operation and discharge was 12 (range 7–23) days.

Long-term postoperative results

The median weight gain recorded 3 months postoperatively was +4·0 (range from −12 to +20) kg ($t = 3{\cdot}13$, $P < 0{\cdot}01$, *Figure 1*). The marked postoperative weight loss (−12 kg) recorded in one patient was secondary to a reduction in preoperative steroid-induced weight gain These weight changes have persisted over subsequent follow-up

Recurrent operations

Four patients have undergone a total of ten operations for further obstructive symptoms (two patients had two operations and two patients had three operations) at 18 (range 12–36) months after their previous strictureplasty Thirteen further strictureplasties were performed. All but one of the previous strictureplasty sites were found to be patent and were not the cause of the obstruction One patient in this group underwent laparotomy for adhesive small bowel obstruction 1 month after her third strictureplasty operation and has been symptom-free thereafter

Of the remaining 20 patients, 13 have been symptom-free following strictureplasty, one requiring division of adhesive small bowel obstruction, 5 years after strictureplasty surgery Three patients have suffered minor attacks of self-limiting colicky abdominal pain and four patients have required a total of six hospital admissions for further medical therapy of recurrent Crohn's disease.

Discussion

The majority of patients with Crohn's disease will undergo surgery during the course of their disease[7,8]. Greenstein *et al.*[9] demonstrated that not only does the rate of recurrence increase with the length of follow-up but also there is a group of Crohn's disease patients who require repeated resections at increasingly frequent intervals. This group is at the greatest risk of developing malnutrition secondary to surgically induced short bowel syndrome[4]. Hellers[2] reported a 1·5 per cent incidence of this syndrome in his series of 102 patients and the Leeds study[1] reported a postoperative weight loss of >12·7 kg in 5 1 per cent of 198 patients undergoing resection for Crohn's disease

The principle of minimal surgery for Crohn's disease is that surgery should be structured to improve both the health and symptoms of the patient, while preserving as much intestine as possible[3,4]. This concept of preserving intestine is based on the understanding that, firstly, Crohn's disease is microscopically pan-intestinal; secondly, once diagnosed the patient is always at risk of relapsing; and, thirdly, recurrence of Crohn's disease has been demonstrated to be independent of the presence of microscopical disease at intestinal resection margins[10,11]. Furthermore, no successful adjuvant medical therapy has been shown to decrease the incidence of recurrence following surgery.

The technique of strictureplasty invited criticism as not only does diseased bowel remain *in situ*, but also the anastomosis is constructed through macroscopically involved intestine. The use of this operation can only be justified if the results prove the procedure to be safe, to improve the health of the patient and to be no worse than conventional excisional surgery.

The patients in this series comprised those with malnourishment (>20 per cent weight loss, serum albumin <30 g/100 ml), those with high activity indices of Crohn's disease, those who required intravenous nutrition and high dose steroid therapy, and those patients who were able to maintain normal bodyweight and nutrition in the presence of colicky abdominal pain.

The fears of early postoperative abscess formation and fistulae following this surgery have proved groundless, despite the facts that in two patients the operation was undertaken through segments exhibiting acute disease and that seven patients had between four and 21 strictureplasties fashioned at one operation.

Furthermore, the long-term benefits of strictureplasty surgery are confirmed by our study as continued nutritional and symptomatic improvement has been maintained in 20 of 24 patients It is interesting that the sites of recurrent obstructive Crohn's disease do not appear to occur in segments of bowel on which a strictureplasty has been previously performed, as illustrated by the four patients in our series who have undergone further surgery.

Other surgeons who have performed this operation for obstructive Crohn's disease have also reported encouraging results[12–15]. Alexander-Williams[12] has performed 148 procedures in 52 patients, 29 of whom had undergone previous excisional surgery. four anastomotic leaks were reported and 60 per cent of patients had an excellent clinical result 6 months postoperatively. However, Kendall *et al.*[16], have reported recurrence of pain in seven of nine patients, four of whom required further laparotomy, and, in three of these cases, further strictureplasties were undertaken The early recurrence of obstructive symptoms following strictureplasty reported in that series was not thought to be because of recurrent disease in strictureplastied bowel[16].

Strictureplasty should be used in conjunction with conventional excisional surgery At Oxford, the annual number of operations performed for Crohn's disease is between 32 and 40. Since its introduction to our unit strictureplasty is performed approximately three times per annum. Thus, we stress the importance of careful operative selection of the lesions most likely to respond well to strictureplasty. Distinction must be made between segments of bowel obstructed either by phlegmonatous Crohn's disease or by fibrotic Crohn's disease. We believe that the former lesions are best treated by 'mini resection'[4] and that if treated by strictureplasty they may well be the site and cause of early postoperative recurrence of symptoms, while the latter lesions are those most amenable to strictureplasty Adherence to these principles has permitted us to undertake strictureplasty in patients with both limited and extensive disease

Whether this operation is as effective, in the long term, as resection of bowel affected by Crohn's disease, remains unanswered. We do not claim that our good results are entirely consequent on strictureplasty since 15 patients underwent simultaneous resections. Nevertheless, we believe that our results demonstrate the procedure to be safe, in particular, with respect to anastomotic failure and fistula formation, we found it to be an effective means of preserving intestine and relieving obstructive symptoms.

We recommend its use, in conjunction with conventional excisional surgery, for patients with obstructive Crohn's disease, and we stress the importance of ensuring that no distal obstruction remains unrelieved for fear of precipitating anastomotic dehiscence at the site of strictureplasty[12,16].

Acknowledgement

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Paper accepted 21 October 1988

Associate Editor

Mr A. E. Young is relinquishing his appointment as Associate Editor of the Journal this month and the increasing workload of the post is reflected in the fact that he will be replaced by not one but two Associate Editors, Professor John Farndon from Bristol and Mr John Murie from Edinburgh.

Tony Young joined the editorial team of *The British Journal of Surgery* partly for his literary and editorial skills, which are considerable, and also to give aid in the birth of our computerized office; the delivery of this latter infant was not without its setbacks, but it is now thriving and we are deeply grateful to Tony for his hard work and common sense during this difficult time. He will not be severing his links with *The British Journal of Surgery* but will remain a member of the Editorial Committee.

Surgical workshop

Br. J. Surg. 1989, Vol. 76, April, 342–343

T tubes: a comparison of virgin, slit, guttered and sculpted design

L. Crnojevic*, J. N. Thompson and
H. A. F. Dudley

*Academic Surgical Unit, St Mary's Hospital, London W2, UK and *Department of Surgery, Army Hospital, Pula, Yugoslavia*
Correspondence to. Mr J. N Thompson, Department of Surgery, Hammersmith Hospital, London W12 0HS, UK

T tube drainage after supraduodenal bile duct exploration remains common practice[1–3], although the general pattern of T tubes commonly used today was first described by Deaver in 1904[4]. Although uncommon, bile peritonitis is a well-recognized event after T tube removal. Corbett *et al.*[5] estimated the incidence following removal of latex T tubes to be 1 in 119 patients. Extrapolated to the UK, such an incidence would imply approximately 50 cases each year, with their attendant morbidity and mortality.

A number of factors have been implicated in the development of bile peritonitis after T tube removal[5–8], including inadequate track formation, the choledochotomy suture technique, technical errors, distal bile duct obstruction and the type of T tube material used. While these and other factors may be important, it is our hypothesis that the force required for T tube removal is the major factor determining whether the bile duct or T tube track is disrupted with consequent bile leakage and peritonitis.

Surgeons vary in the size and design of T tubes they use and also in the surgical modifications they make to commercially available latex rubber T tubes. The aim of this study was to assess the factors influencing the force required for T tube removal, particularly the effect of surgical T tube modification.

Methods

To measure the force required for T tube removal an *in vitro* model was used. Latex rubber Kehr T tubes supplied by Warne Surgical Products, Andover, UK were pulled through circular holes of varying size in a rigid plastic sheet 0·5 mm in thickness. The force on each T tube was gradually increased until the tube was completely pulled through the hole. The maximum force required was measured using a spring balance. For each experiment five T tubes of each size and design were used.

The effect of T tube design

For this study, 16 French gauge (Fr) T tubes with side arms each of 2·5 cm in length were used. Four designs of T tube were studied: virgin (unmodified), slit (side arms cut along their length), guttered (half the circumference of the side arms removed), and sculpted (guttered with two Vs cut out opposite the main stem of the T tube) (*Figure 1*). The tubes were pulled through holes ranging in size from 16 to 30 Fr.

The effect of T tube size

T tubes of size 12, 14, 16, 18 and 20 Fr and of each design (virgin, slit, guttered or sculpted) were used. In each case the tubes were pulled through holes of the same size.

The effect of side-arm length

This was studied using virgin 16 Fr T tubes pulled through holes of 16, 18, 20 and 30 Fr. The force required was measured at each hole size for tubes with side arms ranging from 1 to 5 cm in length.

Results

The effect of T tube design

The effect of T tube design is shown in *Figure 2*. The differences between each design of T tube were significant at the 5 per cent level for all hole sizes using unpaired *t* tests. At all hole sizes, sculpted tubes required approximately 10 per cent of the force needed for virgin tubes.

The effect of T tube size

There was a progressive reduction in the force required for T tube removal with diminution in the size of the T tube (*Figure 3*). This reduction was seen with all four designs of T tube. A reduction in the size of the T tube by 2 Fr significantly reduced the force required for tube removal in 11 of the 16 direct comparisons made in this experiment ($P < 0{\cdot}05$, unpaired *t* tests).

The effect of side-arm length

There was no significant difference in the maximum force required to remove 16 Fr T tubes through holes of 16, 18, 20 and 30 Fr as the side-arm length was reduced by 1 cm lengths from 5 cm to 1 cm.

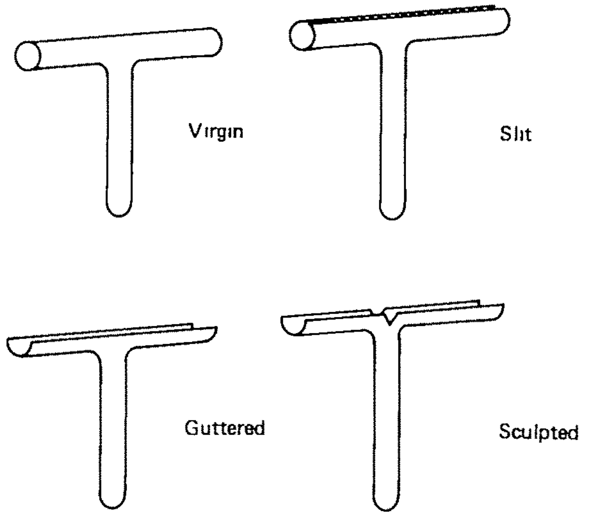

Figure 1 *The four designs of T tube used*

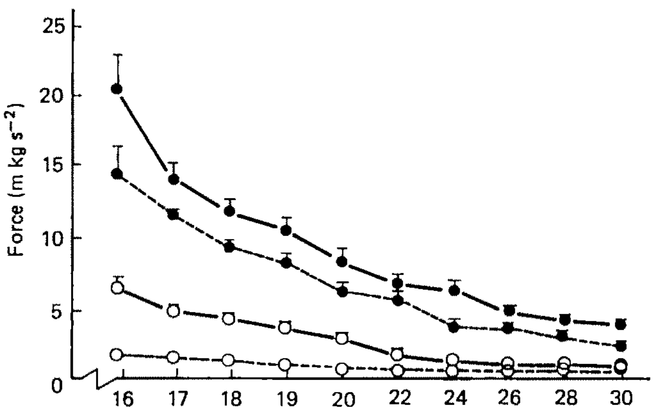

Figure 2 *The effect of hole size and T tube design on the force required for removal of a 16 Fr T tube. ●——●, Virgin, ●---●, slit; ○——○, guttered, ○---○, sculpted. Values are mean ± s.e.m.*

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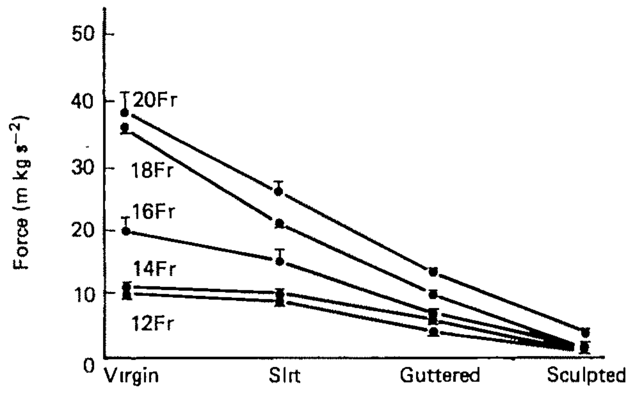

Figure 3 *The effect of T tube size and design on the force required for its removal through a hole of equal size*

Discussion

When considering the complication of bile peritonitis following T tube removal, surgeons have largely focused their attention on the tissue reaction to different materials from which T tubes have been made. It has been held that inflammation is desirable to the formation of a tight sinus track which will prevent leakage at the time of withdrawal. This hypothesis has been used to explain the fact that shortly after the introduction of polyvinyl chloride T tubes, which produce less tissue reaction, several authors reported diffuse bile peritonitis[6,9].

The continued occurrence of biliary peritonitis following removal of latex T tubes[5,7,8] suggests that other factors also play a part. Although this complication probably has a multifactorial aetiology, it would seem reasonable to assume that excessive force should be avoided during T tube removal so that the risk of disruption of the common bile duct or established T tube track is minimized. The present study did not simulate the exact conditions existing during removal of T tubes from patients: the elasticity of the common bile duct differs from the plastic material used, the hole in the common duct may be elliptical rather than circular, and there was no bile to lubricate the T tube. Despite these differences this study shows that the major mechanical obstacle to T tube removal is located at the junction of the side arms with the main stem, and that the resistance to removal caused by this junction is altered substantially *in vitro* by the modifications in T tube design assessed in this study. The sculpted tube effectively eliminates the resistance caused by the junction of the T tube.

The suggestion by radiologists that a large diameter T tube should be used routinely after bile duct exploration to facilitate the later percutaneous extraction of any retained stones should be considered cautiously by surgeons as the larger T tubes required increased force for their removal.

We suggest that to minimize the risk of bile peritonitis after T tube removal, surgeons should opt for a smaller size of T tube where appropriate and, perhaps more importantly, should sculpt their T tubes before placing them in the common bile duct. In addition, the removal of all T tubes should be undertaken with care. It is anticipated that such steps would substantially reduce the continuing surgical morbidity and mortality related to the use of T tubes.

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Sutureless large bowel anastomosis: European experience with the biofragmentable anastomosis ring

C. J. Cahill, M. Betzler*, J. A. Gruwez†, J. Jeekel‡, J.-C. Patel§ and B. Zederfeldt¶

*Kingston Hospital, Kingston upon Thames, UK, *Chirurg Univ Klinik, Heidelberg, FRG, †Department of General Surgery, U.Z K.U L. Leuven, Belgium,‡Department of General Surgery, University Hospital, Rotterdam, The Netherlands, §Department of General Surgery, Hôpital Ambroise Paré, Boulogne B, France and ¶Department of Surgery, University Hospital, Malmo, Sweden*

Correspondence to
Mr C. J Cahill, Department of Surgery, Westminster Hospital, Page Street, London SW1P 2AP, UK

Sutureless colonic anastomosis using a biofragmentable anastomosis ring (BAR) has been evaluated in a prospective randomized comparison with sutures and staples for elective colorectal surgery. One hundred and one patients underwent BAR anastomosis, 85 a sutured anastomosis, and 16 a stapled anastomosis. There were two anastomotic leaks in the patients undergoing BAR anastomosis, seven in patients having a sutured anastomosis, and one in a patient who had a stapled anastomosis. Wound infection occurred in ten BAR patients, ten sutured patients and no stapled patient. There was no statistically significant difference in these or in other postoperative complications between the groups. The BAR was easy to use and is a safe alternative to sutures and staples for large bowel anastomosis.

Keywords: Colon surgery, surgical staples

A significant part of the morbidity and mortality associated with colonic anastomosis results from anastomotic leakage, and surgeons are constantly seeking to improve anastomotic techniques.

Nicholas Senn of Chicago wrote in 1893: 'We have reason to believe that the technique of intestinal suturing remains an unfinished chapter, and that the ideal method of uniting intestinal wounds has yet to be devised'[1]. A technique of sutureless anastomosis was conceived by Denans in Marseilles in 1826[2] which encompassed the inverting technique proposed by Antoine Lembert[3]. However, it was not until 1892 that Murphy designed a 'button' that gained more widespread acceptance[4] (*Figure 1*) This, too, fell from favour because it relied on necrosis for its release from the anastomotic site, and not infrequently it became impacted lower down the gastrointestinal tract. Senn[1] summarized the criteria for a successful sutureless anastomotic device thus: 'Any internal aids to circular suturing should be composed of absorbable material and employed in such a way as not to produce marginal gangrene and with a central opening large enough to allow free faecal circulation'. A bowel anastomosis ring seeking to fulfil these criteria has been devised by Hardy *et al.*[5], and produced by Davis and Geck (Valtrac®; Danbury, Connecticut, USA). This device has been evaluated in a European multicentre prospective randomized trial comparing it with sutured and stapled anastomoses.

Patients and methods

The Valtrac anastomosis ring (BAR) is a biofragmentable device composed of polyglycolic acid polymer and 12·5 per cent barium sulphate. γ-Irradiation both sterilizes the device and facilitates its disintegration at the appropriate time of 16–23 days, barium renders it radio-opaque. It constructs a secure inverting anastomosis with accurate serosa-to-serosa apposition until healing occurs The device then fragments and soft pieces are passed out in the stool.

The device is supplied in 28, 31 and 34 mm external diameter sizes, with a 6 mm open gap-width (*Figure 2*) Closed gap-widths of 1·5 and 2·0 mm are available for the 28 and 31 mm sizes, and closed gap-widths of 2·0 and 2·5 mm are available for the 34 mm diameter BAR to accommodate different thicknesses of bowel wall. A monofilament absorbable purse-string or whip stitch is inserted into the bowel ends to be joined using a modified purse-string instrument (Davis and Geck) or by hand USP 3/0 (2 metric) polyglyconate (Maxon®, Davis and Geck) or polydioxanone (PDS®, Ethicon Ltd, Edinburgh, UK) are suitable for this purpose.

A BAR of appropriate external diameter and gap-width is selected, using EEA® (US Surgical Corporation and Auto Suture UK, Ascot, UK) 'sizers' if desired. The BAR is inserted into the proximal bowel end first by means of the plastic handle provided (*Figure 3a*) The purse-string is tied snugly, but not too tightly as this may cause necrosis and early passage of the intact device. The plastic handle is removed and the BAR is inserted into the distal bowel (*Figure 3b*). Correct alignment of the mesentery is confirmed and the second purse-string is tied The device is closed by index finger and thumb pressure of two hands, 180° apart, and usually results in an audible or palpable click Additional serosal supporting sutures were inserted by some surgeons if complete serosal apposition was uncertain

Two hundred and two patients undergoing elective colorectal procedures were prospectively randomized to undergo anastomosis using either conventional techniques (sutures or staples) or the BAR Randomization was stratified to compare the device with both sutures and staples, and the surgeon elected at operation after resection which 'control' method would be his usual choice. Only then was a randomization envelope opened to select the anastomotic technique. The number of stapled patients was small, and no significant differences emerged between the sutured and stapled groups. All comparisons between groups were made using the χ^2 test with Yates' correction for continuity Informed consent was obtained from all patients taking part, and the trial protocol was approved by the local ethical committee in all the participating hospitals

Anastomotic leakage, wound infection and subacute obstruction rates reported are those detected clinically. No routine radiological contrast studies were performed in this series.

Results

There were no significant differences between the groups of patients, which were well matched for age, sex, incidence of malignancy and inflammatory bowel disease (*Table 1*). Anastomoses constructed are shown in *Table 2*, and the BAR sizes used are shown in *Table 3*. Techniques of bowel preparation and perioperative antibiotic usage are shown in *Table 4*. Adequacy of bowel preparation was reported as excellent or good in 84 per cent of cases, and as poor in only 3 per cent, with no differences between groups.

No intraoperative complications of sutured anastomoses were reported. One stapled anastomosis was unsatisfactory; this was taken down and a sutured anastomosis performed.

Twelve anastomoses using the BAR were technically difficult to complete. One rectum was split with an EEA sizer, and four purse-strings failed using the modified purse-string instrument. The remaining seven problems (6·9 per cent) were specific to

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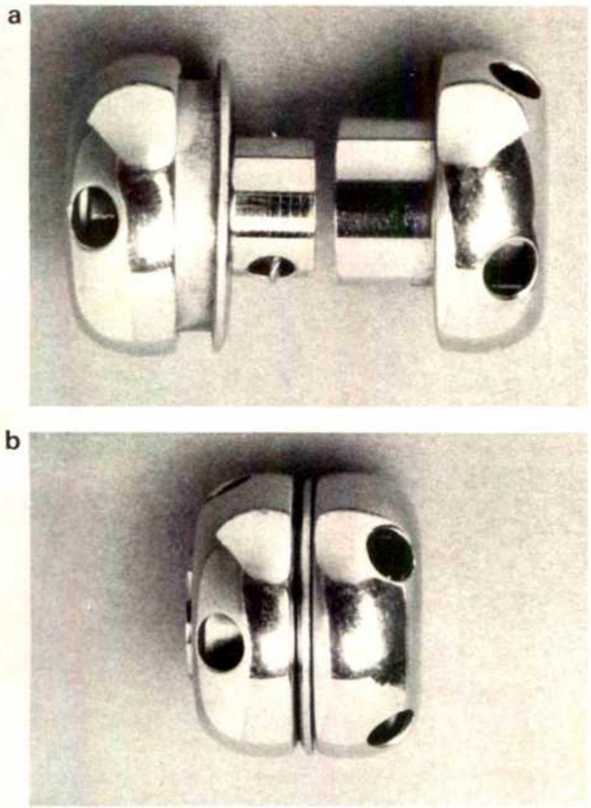

Figure 1 *Murphy's button used formerly in sutureless intestinal anastomosis.* **a** *button open;* **b** *button closed*

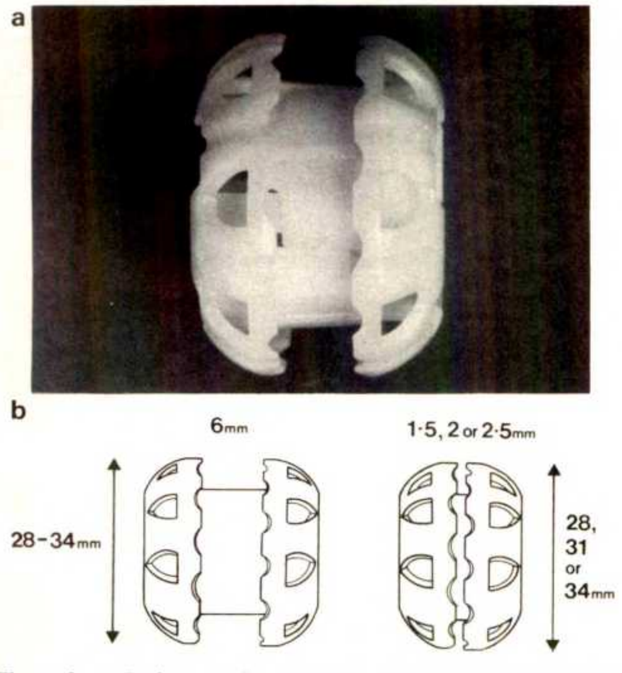

Figure 2 **a** *Biofragmental anastomosis ring (BAR) showing 6-mm gap-width;* **b** *diagrammatic representation of BAR in open and closed positions*

the BAR: in three cases the device was too large to enter the small intestine or colon, or a serosal tear occurred; in two cases thick bowel wall was difficult to place within the 6-mm open gap (*Figure 2*); and in two cases it was difficult to place the device into the second (distal) bowel lumen in the pelvis. A second BAR was successfully inserted after failure of a purse-string but, in four cases of difficulty, BAR anastomosis was abandoned in favour of a sutured (three cases) or stapled (one case) anastomosis. In three of the cases the BAR was too large or tearing occurred, and in the fourth the bowel wall was too thick to permit safe insertion of the device.

There was no significant difference in the postoperative return of bowel function, or the length of hospital stay, in the BAR or control groups.

Twenty-two patients were aware of passing remnants of the BAR. Two complained of some anal discomfort after passage,

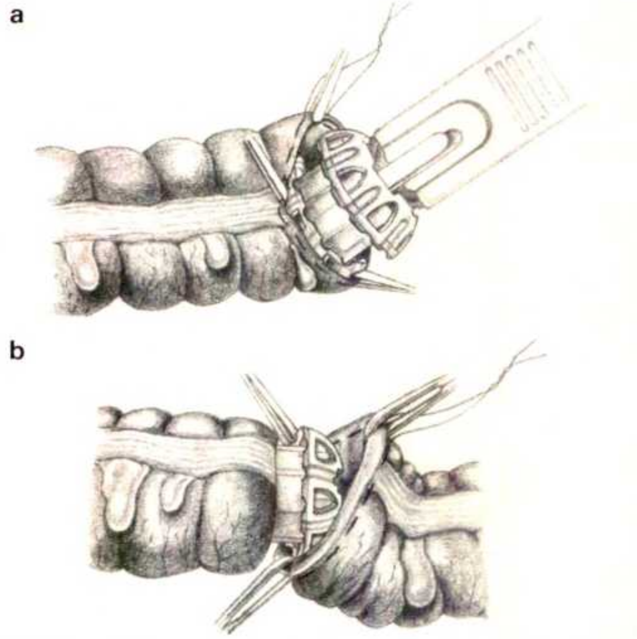

Figure 3 **a** *Biofragmental anastomosis ring (BAR) being inserted into proximal bowel by means of plastic handle;* **b** *BAR being inserted into distal bowel to complete the anastomosis*

Table 1 *Patient details*

	Method of anastomosis		
	BAR ($n = 101$)	Staples ($n = 16$)	Sutures ($n = 85$)
Male	41	7	45
Female	60	9	40
Mean age in years (range)	63·1 (17–88)	66·8 (30–84)	63·3 (18–88)
Malignancy	63	12	54
Inflammatory bowel disease	4	—	4
Diverticular disease	10	1	8

BAR, biofragmentable anastomosis ring

Table 2 *Anastomoses performed*

	Method of anastomosis		
	BAR ($n = 101$)	Staples ($n = 16$)	Sutures ($n = 85$)
Proximal colon			
Ileocolic	30	3	31
Colostomy closure	9	2	7
Transverse colon anastomosis	6	—	7
Distal colon			
Left hemicolectomy	13	1	8
Sigmoid colectomy	40	3	29
Anterior resection	2	6	2
Reanastomosis (Hartmann's operation)	1	1	1

BAR, biofragmentable anastomosis ring

Table 3 *BAR sizes used in sutureless anastomosis*

Bar size	*n*
28 mm × 1·5 mm gap	15
28 mm × 2·0 mm gap	12
31 mm × 1·5 mm gap	35
31 mm × 2·0 mm gap	25
34 mm × 2·0 mm gap	10
34 mm × 2·5 mm gap	4

BAR, biofragmentable anastomosis ring

Table 4 *Bowel preparation and antibiotic usage*

	Method of anastomosis		
	BAR ($n = 101$)	Staples ($n = 16$)	Sutures ($n = 85$)
Bowel preparation			
Mechanical	47	6	31
Laxative	51	12	48
Enema	65	15	51
Antibiotics			
Systemic	74	9	68
Oral	16	1	12

BAR, biofragmentable anastomosis ring

and one BAR became impacted in the anal canal. This had to be broken up to facilitate passage.

Principal postoperative complications are shown in *Table 5*. All five deaths were due to cardiac or respiratory complications, and unrelated to the surgical technique. There was no statistically significant difference in the anastomotic leakage rate from BAR anastomoses (two cases) and control anastomoses (eight cases) but the leakage rate was skewed by an additional surgeon at one hospital whose sutured patients had four anastomotic leaks, while his BAR patients had one leak. This one surgeon was associated with 50 per cent of the anastomotic failures in the study, and his anastomotic leak rate for sutured anastomoses was significantly greater than that of all the other surgeons involved ($\chi^2 = 17{\cdot}6$, d.f. $= 1$, $P < 0{\cdot}001$).

Postoperative subacute small bowel obstruction occurred in six patients: three after anastomosis with the BAR, one after sutured anastomosis and one after stapled anastomosis settled with conservative treatment. One patient in the BAR group required laparotomy on the tenth postoperative day for division of adhesions between the small intestine and the abdominal wound. All episodes of subacute obstruction involved the small bowel, and in no case was there evidence of mechanical obstruction at the level of the anastomosis, whether this was performed using the BAR, sutures or staples.

Discussion

Animal studies in dogs and pigs[5,6] have shown the BAR to be as effective as sutures or staples for construction of a colonic anastomosis. Intraluminal pressures required to disrupt the anastomosis in pigs was greater for the BAR than for sutures or staples[5]. Anastomoses with the BAR had greater vascular congestion than those which were sutured or stapled, with an increased inflammatory response. However, the incidence of necrotic muscle wall at the anastomosis was lowest in the BAR animals at 16 days, and fewer foreign body giant cells and microabscesses were seen than with the other techniques[5]. Decreased residual granulation tissue present at 1 year suggests that the BAR may even be biologically superior to other anastomotic methods.

Early clinical experience from one centre[7] was encouraging, and the present study was set up to evaluate the device by a number of different surgeons in different hospitals. In most cases the device was quick and easy to use. The purse-string sutures can be placed accurately using either the modified Furness clamp or by hand, but unsatisfactory purse-strings must be replaced, as inaccurate placement of the bowel ends within the device may lead to failure of its closure or to an anastomotic leak.

Serosal tearing, by injudicious use of unduly large sizers or use of too large a BAR, also appears to be hazardous as the device works by maintaining serosal apposition. A serosal defect combined with ischaemia of the remaining bowel wall[8] due to pressure from too large a device may have contributed to the two BAR leaks. These hazards may be avoided by careful assessment of luminal size, choice of the appropriately sized BAR, and use of a side-to-end technique particularly for narrow terminal ileum.

The open gap-width of 6 mm made use of the BAR difficult in two patients with very thick bowel wall, and this may at present be a relative contraindication to its use. The device was used in the upper rectum and its use in the middle third is being investigated. There is no transanal insertion technique at present, thus precluding its use for low anterior resection. Development of a transanal introducer, or separation of the device into two parts for individual placement in the bowel ends and subsequent locking, would extend the usefulness of the BAR. There was no difference in the anastomotic leak rate or wound infection rate between the groups. The apparently lower anastomotic failure rate for the BAR may be confirmed statistically by study of larger numbers of patients. One surgeon had a significantly increased anastomotic failure rate; excluding the 14 patients upon whom he operated the anastomotic leak rate for the study (BAR 1, staple 1, suture 3; 5/188 = 2·7 per cent) was acceptable for elective colorectal surgery.

This device produces a safe, rapidly executed anastomosis. The lack of granulation tissue and scarring at 1-year evaluation in animals may indicate its superiority over the stapled anastomosis with its tendency to stricture. Many European surgeons do not usually use staples for intraperitoneal large bowel anastomoses, but the BAR is theoretically attractive for the patient with inflammatory bowel disease, diverticulitis, or impaired healing for other reasons, and further clinical evaluation in these groups is necessary. Animal work has already confirmed the safety of the device in animals given steroids[6], and after irradiation of the bowel[9]. Speed of use for multiple anastomoses is attractive in major intra-abdominal trauma, and in the severely debilitated patient. Further assessment in these groups is awaited.

In 1902, Jeannel commented on Ramaugé's version of Murphy's button: 'I believe I know how to sew, yet I side with the boutonnistes. Is it to be denied that for the average surgeon it is easier to apply an anastomotic button than to suture an anastomosis? And moreover, when the suturists point to the failures of the button, have they forgotten their own failures? Who dares pretend that sutures have not claimed, and will not continue to claim, more victims than the buttons.'[10].

The Valtrac BAR represents a button fulfilling Senn's criteria introduced to current surgical practice, and preliminary assessment is encouraging. Our evaluation of the BAR in

Table 5 *Complications of anastomosis methods*

	Method of anastomosis		
	BAR	Staples	Sutures
Hospital death	2	1	2
Anastomotic leak	2	1	7
Wound infection	10	—	10
Postoperative subacute obstruction	4	1	1

patients undergoing elective colorectal surgery has confirmed its safety and efficacy compared with established techniques. Further evaluation in high risk groups may confirm its superiority, and evaluation in other gastrointestinal anastomoses may extend the indications for clinical use of the BAR.

Acknowledgements

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Surgical workshop

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A more realistic way of practising surgical knots using a surgical glove

A. S. E. Younger and A. A. Gunn

Department of General Surgery, Bangour General Hospital, Broxburn, West Lothian EH52 6LR, UK
Correspondence to: Mr A. A. Gunn

Practising surgical knots outside the operating theatre is an essential part of training. The techniques can be learned from any manual[1], although hours of practice on coffee cup handles and the backs of chairs can still lead to inexpert fumbling in theatre as tissue has a different resistance to pull on suture material.

A blown-up surgical glove with the wrist tied is an excellent simulator of tissue with five fingers on which to tie. As the glove fingers have little resistance to pull, traction across the knot using the index fingers to 'bed' the knot down must be used to prevent the knot being pulled clear. After each knot has been tied, its security and tension can be checked by cutting off the 'finger' distal to the ligature and seeing if the glove deflates.

Further problems arise when the trainee returning to theatre has to tie round held artery forceps. However this can be practised using forceps as in *Figure 1*.

By learning the technique trainees will avoid pulling their sutures off vessels, thus gaining their own confidence and that of their supervisors.

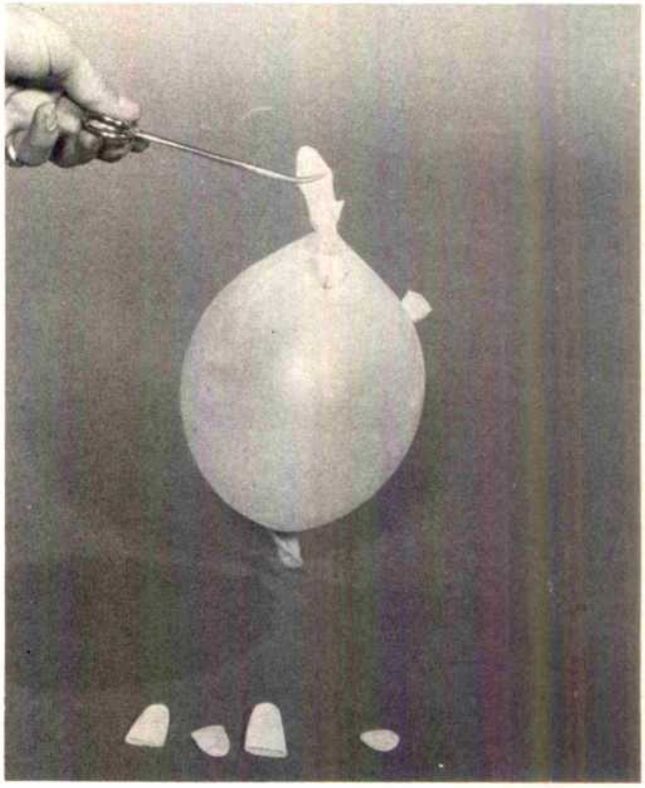

Figure 1 *Four secure knots on four glove fingers. The use of artery forceps is shown*

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Stapling technique for pouch–anal anastomosis without the need for purse-string sutures

N. S. Williams

Surgical Unit, The London Hospital, Whitechapel, London E1 1BB, UK

Correspondence to:
Professor N. S. Williams

Pelvic pouch–anal anastomosis for the surgical treatment of ulcerative colitis is now an established technique[1,2]. The anastomosis is invariably performed trans-anally after sleeving the pouch through a short, denuded rectal stump. In an attempt to simplify the operation and to improve function, some authors have performed an end-to-end stapling anastomosis between the ileal pouch and the anal canal, eliminating the need for mucosectomy[3,4]. Similarly, colonic pouches have also been constructed and anastomosed trans-anally to improve function after low anterior resection[5,6]. The latter anastomoses have all been performed manually. We report a technique using a circular stapling instrument, which can be used either for colonic pouch–anal or for ileal pouch–anal anastomosis. The technique eliminates the need for distal and proximal purse-string sutures and thus reduces the associated risks.

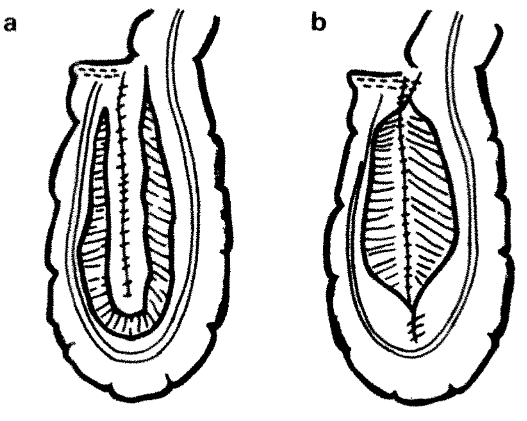

Figure 1 **a** *A J colonic pouch is constructed from the descending colon;* **b** *a defect is left in the anterior wall*

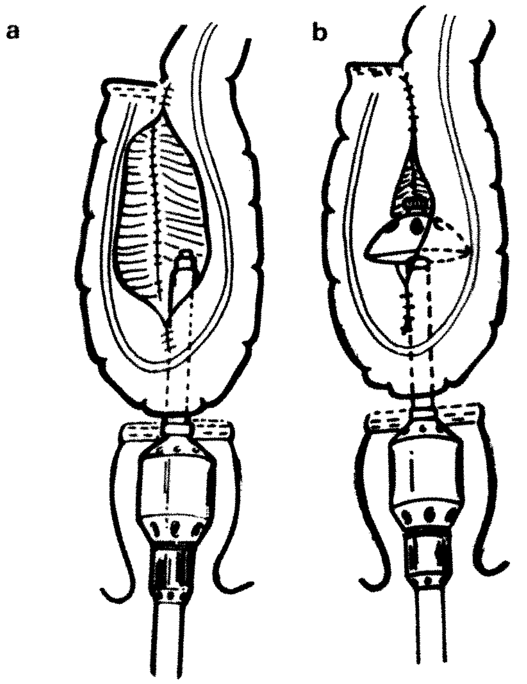

Figure 2 **a** *The shaft of the stapling gun without the head is inserted first through the stapled rectal stump and then through the apex of the pouch, so that it appears through the anterior wall defect of the pouch.* **b** *The head of the gun is screwed onto the shaft*

Technique

The description will concentrate on the colonic pouch procedure since end-to-end stapled colonic pouch–anal anastomosis has not been reported previously. The left colon and distal half of the transverse colon are mobilized in the usual way for a low anterior resection. The rectum containing the carcinoma is mobilized down to the pelvic floor. The dissection encompasses all the mesorectum, as described by Heald *et al.*[7], and allows a minimum distal margin of clearance of 2 cm (Reference 8). Division of the anococcygeal attachments allows the rectum to be lifted forwards between the two levator muscles. The rectum is strongly retracted upwards and a right-angled clamp is applied just above the proposed level of transection. The rectal stump is then irrigated with a cancericidal agent (1 per cent cetrimide solution). An appropriate transverse stapling instrument is applied to the taut rectum below the right-angled clamp at the level of the levators, and is fired. The transverse stapler can be applied at an even lower level if an assistant exerts strong upward pressure by a fist inserted between the ischial tuberosities. If any difficulty is experienced in applying the stapler, the right-angled clamp can be removed and then re-applied after the stapler has been fired. The rectum and left colon are then excised as for a conventional anterior resection. A J colonic pouch is partially constructed (6-cm limbs) manually after first ensuring that it will reach the pelvis. The central part of the anterior wall of the pouch, however, is not completed, thus leaving a defect (*Figure 1a* and *b*).

The shaft of the disposable circular stapling gun (size 28 or 30 mm) without the head is inserted through the anorectal stump by an assistant, so that it emerges through the anterior or posterior wall as far away from the transverse stapled line as possible, although this is not crucial. The gun is racked open to its fullest extent. A stay suture is placed on the apex of the pouch at the limit of the anterior suture line. A long artery forceps is inserted through the defect in the anterior wall of the pouch and gently pushed through the apex of the pouch, well away from the suture lines. Using the artery forceps as a guide, the shaft of the gun is passed into the lumen of the pouch to emerge through the anterior wall defect (*Figure 2a*). The head of the instrument is then screwed securely to the shaft (*Figure 2b*). The anterior wall of the pouch is completed with the head of the gun within the pouch lumen (*Figure 3*). The head and the shoulder-piece of the gun are then racked together in the usual manner (*Figure 3*). Gentle pressure applied by the assistant upwards on the gun enables the anorectal stump to be seen clearly. Similarly, gentle traction upwards on the colonic pouch by the abdominal surgeon allows both the pouch and the anorectal stump to be approximated without extraneous tissue interposing between them, and traction anteriorly on the stay suture ensures that the anastomosis is constructed well away from the suture lines of the pouch. The gun is fired when apposition is complete, and removed in the usual way. The integrity of the 'doughnuts' is then checked. The procedure can be modified for an ileal pouch, whether it be of the J , triplicated or W configuration.

Although the technique described uses the conventional circular stapling instrument, the operation can be performed with little modification using the new Premium EEA® (US Surgical Corporation and Auto Suture UK, Ascot, UK) instrument. If the latter is used, the shoulder-piece of the instrument with its central, pointed pin *in situ* is inserted into the anorectal stump so that the pin penetrates the wall. After the instrument has been fully racked open, the central pin is removed. The separate anvil pin, together with its attached head, is inserted into the pouch through the anterior wall defect, and the pin is gently pushed through the apex of the pouch away from the suture lines of the pouch. The anvil pin is then inserted into the hollow end of the main shaft of the instrument as it emerges from the anorectal stump. It is important to ensure that the anvil pin is pushed home and clicked into position. The head and shoulder-piece are then racked together in the usual way, and the gun is fired.

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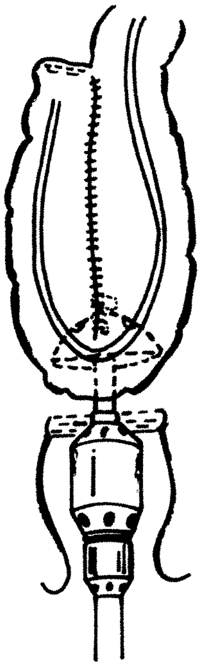

Figure 3 *The gun is withdrawn into the pouch and the anterior wall defect is closed. The head and shoulder-piece are racked together and the gun is fired*

Discussion

Recent data on pathology[9] have shown that microscopic radial spread of rectal cancer is common and that surgeons frequently leave these deposits behind, even when they believe at the time of operation that they have performed a curative resection. To ensure the removal of as much microscopic disease as possible, it seems logical to excise all the mesorectum, irrespective of the height of the tumour from the anal verge[7]. Unfortunately, such a manoeuvre may leave behind an ischaemic rectal stump. To prevent this problem, it is perhaps safer to remove the entire rectum and to leave just the anal canal. Although anastomosis of colon to a short anal cuff results in continence, patients often suffer severe frequency of bowel action[10]. The cause seems to be a combination of low resting anal pressure and reduced 'rectal capacity'[11]. To overcome the problem, Lazorthes *et al.*[5] and Parc *et al.*[6] suggested the use of a J colonic pouch, which they anastomosed via the peranal route[12] to the anal canal. Their technique overcame the problem of reduced rectal capacity, and function has been shown to be superior to a straight coloanal anastomosis[13]. Nevertheless, since their technique requires that the anal sphincter be stretched for some time during construction of the anastomosis, it is likely that damage will still be inflicted on the sphincteric mechanism. To eliminate this problem, it was decided to construct the pouch-anal anastomosis by end-to-end anastomosis using the stapling gun. Such an approach has been found to produce better functional results when ileal pouches have been anastomosed directly to the anal canal in patients with ulcerative colitis[4]. To simplify the technique even further, and to ensure a secure stapled anastomosis, the original technique has been modified by eliminating the need for purse-string sutures.

The construction of a secure stapled anastomosis relies on the accuracy of placement of the purse-string sutures to each end of the bowel lumen to be anastomosed. The suture may not run smoothly through the tissues when the knot is tied, and consequently the tissue is not applied satisfactorily to the shaft of the instrument. Even if the purse-string suture does run smoothly, tissue may be so bunched up in the gap between the shoulder-piece and the head that a complete circumferential anastomosis is not possible. The purse-string may cut out when tied, or may snap, necessitating re-insertion. To avoid some of these problems, several authors[14–16] have eliminated the distal purse-string by transverse stapling of the distal anorectal stump. However, through necessity the proximal purse-string was retained. The formation of a pouch, whether colonic or ileal, provides the opportunity also to eliminate the proximal suture and to make the anastomosis even more secure.

The technique described can be performed using either the conventional circular stapling instrument or the new Premium EEA. The latter instrument has been used on several occasions and, although it is simple to use, it only marginally streamlines this particular technique. A possible future complication is the greater propensity to anastomotic dehiscence owing to the possibility of devascularization of the pouch apex. To date, the first 20 patients treated in this way have had no more anastomotic complications than those patients with a conventional anastomosis. Clearly, however, carefully controlled data will be required before this question can be answered fully.

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An improved technique of J pouch construction and ileoanal anastomosis

W. A. Brough and P. F. Schofield

Department of Surgical Gastroenterology, Withington Hospital, Manchester, UK

Correspondence to: Mr P. Schofield, Teaching Unit 5,
Withington Hospital, West Didsbury, South Manchester
M20 8LR, UK

The technique for the construction of a J shaped ileal reservoir with ileoanal anastomosis after proctocolectomy was first described by Utsunomiya *et al*[1] in 1980. This technique requires four enterotomies to allow entry of a GIA50® (US Surgical Corporation and Auto Suture UK, Ascot, UK) stapling device to create the pouch.

We have modified this and combined it with other surgical techniques to allow a simple and rapid pouch construction and ileoanal anastomosis.

Method

J pouch construction

The 40 cm loop of terminal ileum is fully mobilized. Three chromic catgut stay sutures are placed in the antimesenteric border of the bowel to approximate the two 20-cm limbs of ileum. A Prolene® (Ethicon Ltd., Edinburgh, UK) purse-string suture is inserted at the apex of the J, and an enterotomy is made in the centre of the purse-string (*Figure 1*). The new GIA90® (US Surgical Corporation and Auto Suture UK) stapling instrument is introduced through the enterotomy and the instrument is 'fired' (*Figure 1*). Through a second enterotomy in the proximal part of the afferent limb a second GIA90 stapling device is inserted and fired after ensuring an overlap of the two suture lines to avoid a mucosal bridge from a segment of unstapled pouch. Alternatively, by telescoping the bowel repeated applications of the GIA50 stapler can be made through the same enterotomy at the apex of the J allowing fast, easy and accurate construction of the pouch[2]. The result is a large J pouch with good mucosal apposition and a single enterotomy at the apex of the J. The distal end of the ileum is anastomosed end-to-side with the pouch using two layers of chromic catgut to avoid stenosis of the pouch entrance.

Ileoanal anastomosis

The rectum is fully and carefully mobilized to the pelvic floor by close dissection in all four quadrants. The bowel is divided in the mid-rectal region with no attempt at this stage to remove excess rectum. The anus and remaining rectum are everted[3,4] and traction is applied to demonstrate the dentate line. A Prolene purse-string suture can then be accurately placed 1 cm above the dentate line (*Figure 2*). This allows a 1 cm margin for the resected 'doughnut' after the residual rectum has been excised up to the purse-string. This negates the need for mucosal proctectomy. The purse-string is then passed through the anus to the abdominal surgeon and the anus is inverted.

The detachable anvil of the new Premium curved EEA® (US Surgical Corporation and Auto Suture UK) stapling gun (size 31 mm) is passed through the enterotomy of the J pouch and secured with the previously placed Prolene purse-string suture (*Figure 3*). The Premium curved EEA gun without the anvil is introduced into the anus in the fully extended position. The purse-string in the lower rectum is then tightened around the lower head of the Premium gun. The detachable anvil and J pouch are then passed into the pelvis and the anvil is 'locked' home into the central column of the stapling gun (*Figure 4*). The stapling device is tightened and fired. The result is a large stapled ileoanal anastomosis.

Discussion

The GIA50 stapler for constructing a J shaped pouch is not original[1]. However the modified technique of only one enterotomy[2] in combination with the longer GIA90 stapler allows rapid and accurate construction of the pouch. The single enterotomy is then incorporated into the ileoanal anastomosis. In contrast to Slutzki *et al.*[4], we use a Prolene purse-string suture in the apex of the J pouch to secure the detachable anvil of the Premium curved EEA gun.

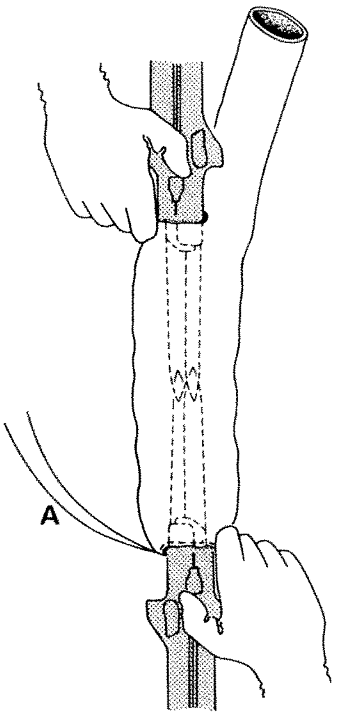

Figure 1 *Formation of J pouch with two GIA90 stapling devices. The Prolene purse-string (A) is placed at the apex of the pouch*

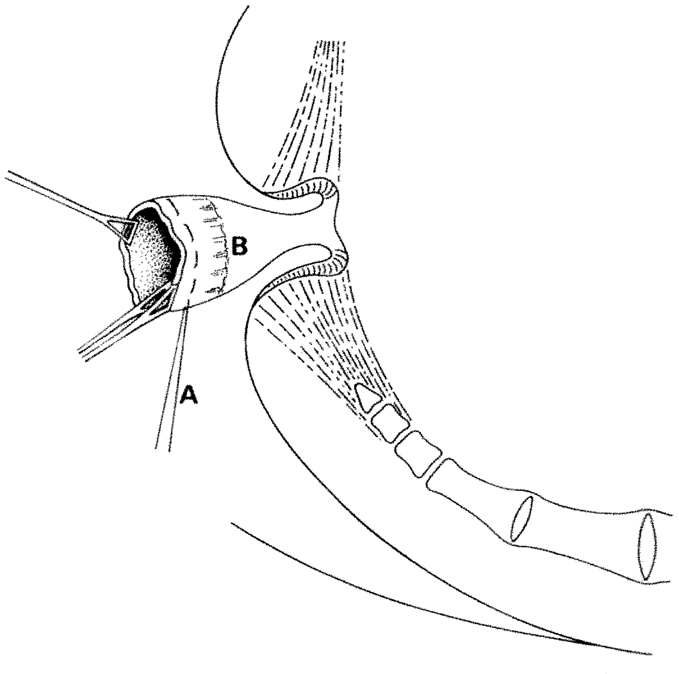

Figure 2 *Everted rectum and anus. The Prolene purse-string (A) in situ 1 cm above the dentate line (B)*

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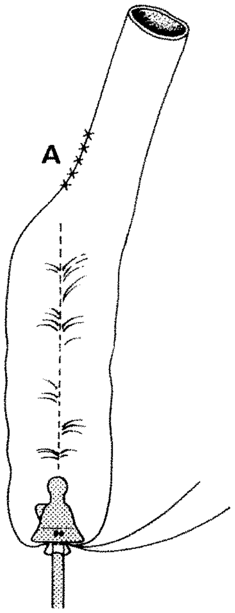

Figure 3 *Insertion of the detachable anvil into apex of J pouch. The distal limb (A) has been anastomosed to the afferent limb*

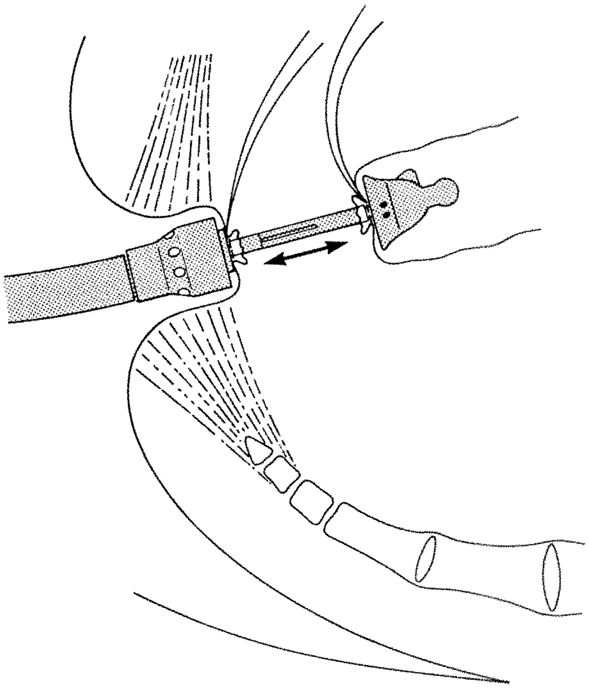

Figure 4 *The Premium curved CEEA gun in position with the J pouch containing the detachable anvil brought into the pelvis*

Eversion of the anus is not a new technique and does not alter anal function[3,4]. In this operation eversion of the anus facilitates the placing of the lower purse-string which allows the remaining mucosa to be removed as a 'doughnut' of rectum. In contrast to the technique for performing low anterior resection of the rectum we find it easier to invert the anus after placing the purse-string because the lower head of the gun does not completely enter the anus when in the correct position for firing. Tying of the lower purse-string is made easier as the detachable anvil is not in position. After securing a good distal purse-string the anvil and J pouch are approximated. This modified technique allows: (1) rapid construction of a J pouch, (2) accurate and easy placing of both purse-string sutures, and (3) removes the need for mucosal proctectomy.

We have used this technique in the formation of ten ileoanal anastomoses. Water soluble contrast studies at 7 days outlined a large pouch with no leaks. This may suggest that a covering ileostomy is not necessary. Satisfactory 'porridge tests' (ability to retain 180 ml semisolid porridge) confirmed continence in all cases before closure of the ileostomy. Early results show that patients are continent at night with a median stool frequency per 24 h of 5 (range 3–9). Anal manometry is within the normal range. This method of proctocolectomy and ileoanal pouch construction is rapid, safe and shows promising early results.

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352-355

Psychiatric screening for patients with faecal incontinence or chronic constipation referred for surgical treatment

S. E. Fisher, K. Breckon, H. A. Andrews* and M. R. B. Keighley

Department of Surgery and
**Gastroenterology, The General Hospital, Birmingham, UK*
Correspondence to:
Professor M. R. B. Keighley,
The Clinical Teaching Block,
The General Hospital, Birmingham
B4 6NH, UK

Fifty patients attending for surgical treatment of chronic constipation (n = *21*) *or faecal incontinence* (n = *29*) *were studied using two psychiatric screening tests: the Hospital Anxiety and Depression (HAD) scale and the General Health Questionnaire (GHQ). Each patient was assessed preoperatively and 6–12 months postoperatively. Results were compared with age and sex-matched controls* (n = *50*)*. Constipated patients had significantly higher HAD depression scores compared with controls (median and range): 6 (2–12)* versus *4 (0–8),* $P < 0.05$*. Constipated patients who were improved by operation* (n = *13*) *had significantly lower preoperative HAD anxiety scores compared with those who were not improved* (n = *8*)*: 8 (3–14)* versus *15 (10–19),* $P < 0.01$*; they also had significantly lower HAD depression scores: 4 (2–12)* versus *7 (5–11),* $P < 0.05$*. Using these parameters incontinent patients did not differ from controls, but patients who had a bad result after operation* (n = *15*) *had significantly higher HAD anxiety scores than those who obtained clinical benefit* (n = *14*)*: 10 (2–15)* versus *6 (2–12),* $P < 0.05$*; HAD depression scores were also greater: 5 (2–15)* versus *3 (0–9),* $P < 0.05$*; and GHQ scores were greater: 12 (0–47)* versus *4 (0–41),* $P < 0.05$*.*

Keywords: Incontinence, constipation, psychiatric screening

Some patients with constipation or incontinence have a history of anxiety or depression. Although a functional component is recognized in the irritable bowel syndrome[1,2], patients with chronic constipation or faecal incontinence have not been subject to such rigorous psychiatric assessment. Most coloproctologists are aware that patients with chronic constipation are emotionally labile and may exaggerate their symptoms; some patients may have a personality disorder and a few have underlying psychiatric disease. These features appear to be less common in patients with faecal incontinence, and emotional factors are often considered to be secondary to the humiliation experienced by their physical disability. We have investigated the value of psychiatric screening tests in predicting the outcome of surgical therapy in these two disorders of defaecation.

Patients and methods

We have carried out a prospective study amongst 21 constipated and 29 incontinent patients. Screening for anxiety or depression was performed using the Hospital Anxiety and Depression (HAD) questionnaire and the General Health Questionnaire (GHQ)[3,4] scales before and after surgical treatment by one person. Results in patients were compared with age and sex-matched controls. Controls consisted of patients with other unrelated disorders: gallstones, varicose veins and impacted wisdom teeth. Controls completed their questionnaires under the same conditions as the patients. Results were not analysed until completion of the study since we did not wish to modify our surgical decisions on the results of the questionnaires. The surgical procedures offered to patients were based upon clinical and physiological assessment of anorectal function using anal and rectosigmoid manometry, electromyography, passage of transit markers and videoproctography[5-8].

All patients entering the study had been referred for surgical treatment. Underlying medical conditions or drug therapy leading to constipation or incontinence had been excluded, and conservative therapy had been unsuccessful in all patients. No patient was receiving psychiatric therapy when entered into the study.

From 6 to 12 months after operation repeat assessment was performed using the HAD and GHQ scales. The outcome of operation was based on assessment by an independent observer who was unaware of the results of the HAD and GHQ scores.

The HAD scale consists of seven questions relating to symptoms of anxiety and a further seven relating to symptoms of depression. Four alternative responses are available for each question and a score of between 0 and 3 is awarded depending on the option chosen by the patient. By adding the scores a numerical rating for anxiety and depression is obtained.

The GHQ consists of 60 questions with four options per question. These are arranged to show increasingly abnormal symptoms from left to right. The two left-hand columns score 1 and both right-hand columns score 2. The scores are added to give an overall psychiatric rating. No attempt was made during this study to assess the reproducibility of the tests used.

Results were compared using the Mann–Whitney *U* (two-tailed) test.

Results

Of the 50 patients recruited to the study, follow-up questionnaires 6–12 months after operation were completed by 46; three failed to keep their follow-up appointment and one patient had been admitted to a psychiatric hospital because of severe depression.

Comparison between preoperative scores for each group and controls are shown in *Table 1*.

Constipated patients had significantly higher HAD depression scores than controls (*Figure 1*) ($P < 0.05$). Constipated patients who had a good result following operation did not differ from controls (*Figure 2*), whereas those who had a poor outcome differed significantly from controls for all three parameters (*Figure 3*). A comparison was made between those patients who benefited from surgery and those who did not; those with a poor functional result had significantly higher anxiety ($P < 0.01$) and depression ($P < 0.05$) HAD scores than those who did well (*Figure 4*).

When the same analyses were applied to the incontinent patients, no significant differences were demonstrated between

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Table 1 *Preoperative results*

Patient group	Hospital Anxiety and Depression scale: Anxiety score	Hospital Anxiety and Depression scale: Depression score	General Health Questionnaire score
Constipated			
All patients	11 (3–19)	6 (2–12)	18 (4–48)
Controls	7 (1–17)	4 (0–8)*	14 (0–53)
Good result	8 (3–14)	4 (2–12)	8 (4–42)
Controls	8 (1–14)	3 (0–8)	14 (1–53)
Poor result	15 (10–19)	7 (5–11)	33 (5–48)
Controls	7 (3–17)	2 (0–8)†	10 (0–31)†
Incontinent			
All patients	8 (2–15)	4 (0–15)	10 (0–47)
Controls	9 (3–17)	4 (0–14)	15 (0–29)
Good result	6 (2–12)	3 (0–9)	4 (0–41)
Controls	9 (3–17)	5 (1–13)	18 (0–25)
Poor result	10 (2–15)	5 (2–15)	12 (0–47)
Controls	9 (6–17)	4 (0–14)	14 (0–29)
Constipated			
Good result	8 (3–14)	4 (2–12)	8 (4–42)
Poor result	15 (10–19)‡	7 (5–11)*	33 (5–48)
Incontinent			
Good result	6 (2–12)	3 (0–9)	4 (0–41)
Poor result	10 (2–15)*	5 (2–15)*	12 (0–47)*

Values are medians with range in parentheses. * $P<0\cdot05$; † $P<0\cdot02$; ‡ $P<0\cdot01$

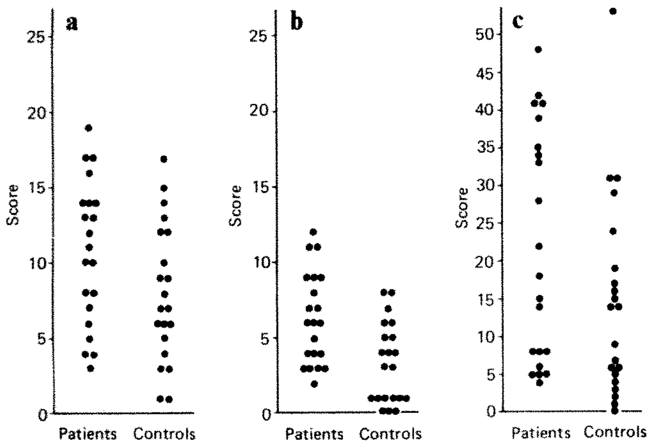

Figure 1 *Preoperative scores in the total group of constipated patients and controls.* **a** *Hospital Anxiety and Depression (HAD) scale, anxiety scores,* **b** *HAD scale, depression scores,* **c** *General Health Questionnaire scores*

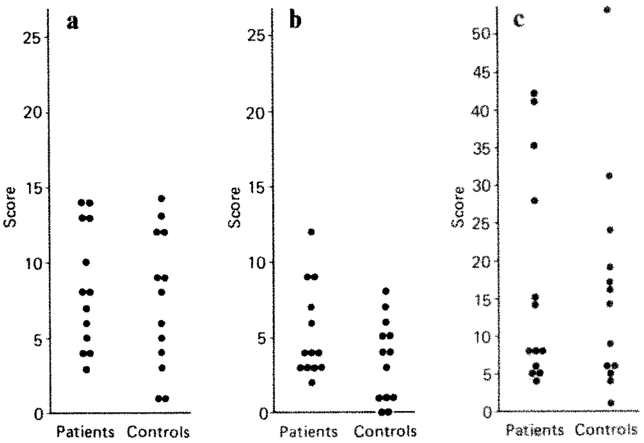

Figure 2 *Preoperative scores in constipated patients who were improved by surgery.* **a** *Hospital Anxiety and Depression (HAD) scale, anxiety scores,* **b** *HAD scale, depression scores,* **c** *General Health Questionnaire scores*

the patients and controls (*Figure 5*). Comparison between those who did well and those who did not showed that clinical benefit was associated with significantly lower HAD anxiety scores ($P<0\cdot05$), lower HAD depression scores ($P<0\cdot05$) and significantly lower GHQ scores ($P<0\cdot05$) (*Figure 6*).

Comparison between preoperative and postoperative scores indicated that none of the groups changed significantly during follow-up. There was no correlation between any of the scores and the physiological data obtained during assessment of anorectal function.

Discussion

The role of psychological and emotional factors in the aetiology of organic disease remains unclear. In the field of gastroenterology most attention has been focused on the irritable bowel syndrome. In a recent review, Creed and Guthrie[9] discussed psychological factors in irritable bowel syndrome. When a psychiatric disorder is diagnosed in a patient with organic symptoms it is possible that the patient may have developed both simultaneously, that the psychiatric disorder may precipitate fixation on organic symptoms, or that the presence of chronic organic symptoms may have an effect on the patient's behaviour.

In this study all patients had evidence of clinically important abnormalities of anorectal function. Our study was designed to determine whether there was any evidence of emotional disturbance amongst patients with incontinence or chronic

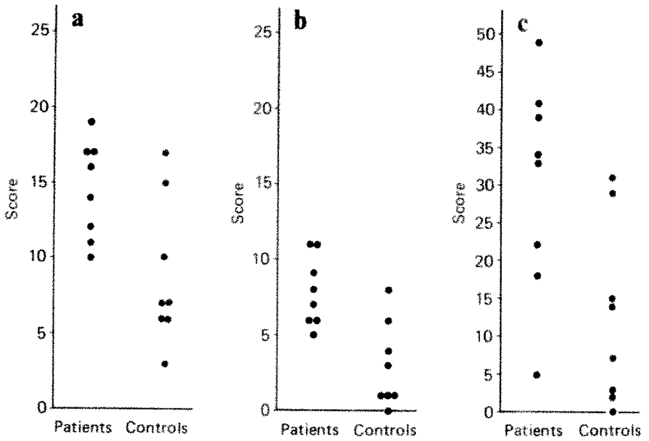

Figure 3 *Preoperative scores in constipated patients who were not improved by surgery.* **a** *Hospital Anxiety and Depression (HAD) scale, anxiety scores,* **b** *HAD scale, depression scores,* **c** *General Health Questionnaire scores*

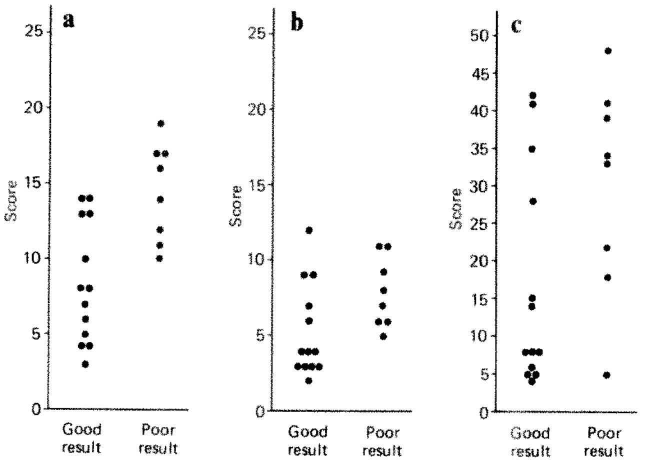

Figure 4 *Scores for constipated patients with good results and with poor results.* **a** *Hospital Anxiety and Depression (HAD) scale, anxiety scores,* **b** *HAD scale, depression scores,* **c** *General Health Questionnaire scores*

constipation compared with controls who had a normal bowel habit. In particular we wished to ascertain whether the operation had any effect on these parameters of anxiety and depression and to identify whether patients who did badly after the operation could be identified preoperatively.

Both screening tests have been developed as self-assessment scales to detect emotional and psychiatric traits. The HAD scale has been designed specifically for use in hospital patients as a means of identifying states of anxiety and depression. The questions are structured so that symptoms which may be of organic or psychiatric origin are excluded; hence the questionnaire is valid for use in patients with physical symptoms. These scales can be used both to study populations and to identify individuals who might benefit from a more comprehensive psychiatric assessment.

The GHQ identifies non-psychotic abnormalities without attempting to provide a specific diagnosis. The 60 questions are grouped. Some are largely somatic symptoms and others are psychiatric. This can lead to difficulties in interpreting high scores in patients with organic illness. The GHQ is a useful assessment of population differences and may also be used to screen individuals. The scale assesses severity of symptoms, but Goldberg[4] reported improved sensitivity and specificity when both minor responses were graded 0 rather than using sequential scores from 1 to 4.

This study suggests that incontinent patients have a similar emotional profile to age and sex-matched controls. Patients who did badly after postanal repair for faecal incontinence had significantly higher preoperative scores for all three parameters than those in whom continence was restored. This finding might be explained if patients with high score have the irritable bowel syndrome since it is known that if episodes of unheralded diarrhoea persist after operation clinical results are poor[10]. Alternatively, persistently high scores may reflect a group of patients who feel socially isolated because of persistent faecal incontinence, particularly as many realize that they may need a permanent stoma. There was no deterioration in the scores of anxiety and depression after operation in patients who had a poor clinical outcome. Hence it is unlikely that preoperative expectations and subsequent disappointment in the outcome is relevant. Since the status of these patients is independent of the operation, it is concluded that preoperative differences may predict the outcome of surgical treatment in incontinent patients.

Constipated patients had significantly higher depression scores preoperatively than controls. It also became clear that constipated patients who fared badly after surgery had abnormal preoperative scores for each parameter tested when compared with controls and with the patients who did well. A review of the scores for individual patients indicates that all eight patients having a poor surgical result had sufficiently high HAD scores to recommend a more thorough psychiatric assessment. This compares with only four of 13 with a good result and six of 21 controls. Probably because of its greater somatic content, the GHQ was less selective than the HAD

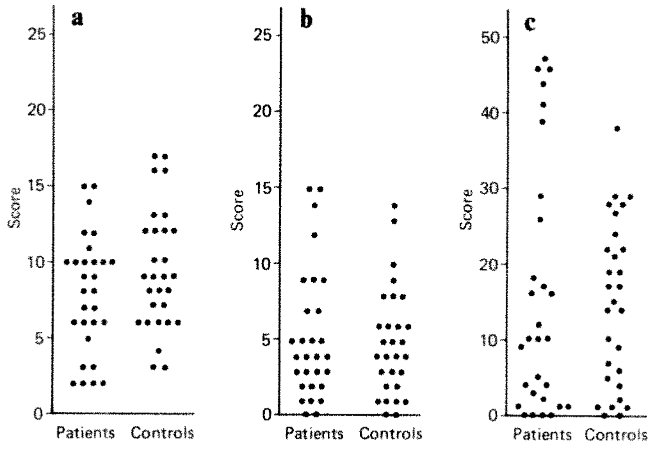

Figure 5 *Scores for all incontinent patients.* **a** *Hospital Anxiety and Depression (HAD) scale, anxiety scores,* **b** *HAD scale, depression scores,* **c** *General Health Questionnaire scores*

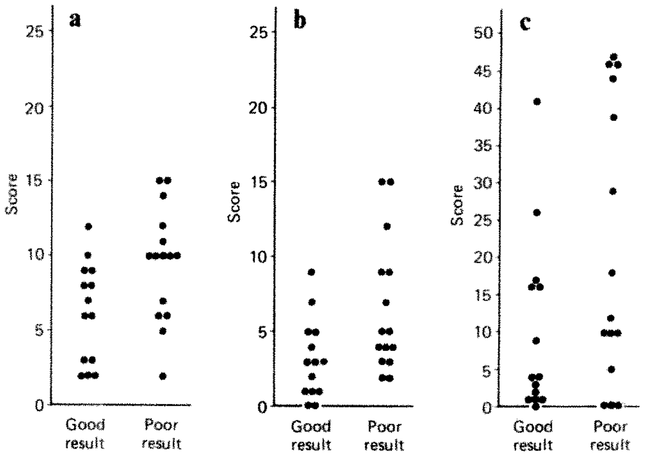

Figure 6 *Scores for incontinent patients with good results and with poor results.* **a** *Hospital Anxiety and Depression (HAD) scale, anxiety scores,* **b** *HAD scale, depression scores,* **c** *General Health Questionnaire scores*

scale. The GHQ identified seven out of eight of the group who had a poor surgical result but also six of 13 patients who did well and 11 of 21 controls who might have merited further psychiatric assessment.

It may be argued that the abnormalities detected in this short-term study were the result of acute stress associated with hospital admission and surgical treatment. If this were so, all groups would be expected to have similar scores, and scores would be expected to change to a lower level after successful surgery. This was not the case. No group showed a significant change between preoperative and follow-up scores. It seems more probable that the psychiatric symptoms identified by screening are not caused by the patient's gastrointestinal disorder. An attempt was made to correlate the severity of symptoms and the degree of physiological abnormality with psychiatric score, but no correlation was found. This again suggests that the presence of psychiatric disturbance is associated with a group of patients who fared badly after surgery.

There is a well-defined group of constipated and incontinent patients who do not respond to conventional surgical treatment and who may be identified preoperatively by psychiatric screening. Thorough assessment is advised in patients with high HAD scores who are constipated since there is a recognized correlation between psychiatric disorders and either outlet obstruction or colonic inertia[11,12].

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Anorectal physiology measurement: report of a working party

M. R. B. Keighley,
M. M. Henry,
D. C. C. Bartolo and
N. J. McC. Mortensen

Correspondence to:
Professor M. R. B. Keighley,
Department of Surgery, 4th Floor,
Queen Elizabeth Hospital,
Edgbaston, Birmingham B15 2TH,
UK

A 2-day meeting was held in Bristol on 5 and 6 July 1988 immediately before the Tripartite meeting of the Surgical Research Society in order to discuss methods and identify areas of agreement with regard to measurement of indices of anorectal physiology. The following report highlights our findings.

Keywords: Anorectal physiology, manometry, sensation, electromyography, videoproctography

Anal manometry

Methods must be stated clearly when reporting the results of anal manometry. If perfused catheters are used the internal diameter of the tubing, its consistency and the size and site of side openings must be recorded. The radial orientation of side holes must be described. The description of the method should indicate whether the technique is one of station pull-through or whether recordings were made by continuous withdrawal, in which case the speed of withdrawal must be recorded. Methods must indicate the rate of infusion, the hydraulic delivery system and the length of the catheter. The commonest method for recording anal pressures is to use a closed water-filled balloon probe. Microtransducers have been used but they fail to correct for radial change and they are expensive.

We could find no consensus on a uniform recording system for anal manometry as the methods used will be influenced by the parameters that need to be assessed. However, damping and inaccuracies over the higher pressure range are recognized with water-perfused catheters. Air-filled balloons are probably the most reliable method for routine manometry. It is recognized, however, that there is a reluctance to change the system of recording if long-term longitudinal studies are needed. For this reason it is accepted that a closed water-filled balloon probe fulfils the requirements for most anal manometry.

It was agreed that anal pressures should be recorded in kilo Pascals (100 cm of water = 9·8 kPa).

It was agreed that maximum resting anal pressure (MRP) should be used to denote the highest recorded pressure at any site in the anal canal at rest.

It was agreed that maximum squeeze pressure (MSP) should be used to denote the highest recorded pressure at any site in the anal canal during maximum pelvic floor contraction.

Rectal sensation

Rectal sensation can be tested by infusion or by incremental volumes of air introduced into a male condom or party balloon mounted on a catheter inserted in the rectum. The sensory response depends on the method used and the position of the patient; both should be stated.

Rectal compliance

It was agreed that the proctometrogram was the best method of measuring compliance. A balloon probe or a microtransducer is inserted inside a male condom and placed in the rectal ampulla. The balloon is continuously perfused with water at 37°C using a constant infusion pump at a rate of 60 ml/min. Compliance is recorded in millilitres per kiloPascal over a volume of between 0 and 1 litre depending on the patient's tolerance. This method was considered to be superior to measurements using insufflation of increments of air into a balloon as results vary with the speed of introducing air and a step-wise change is artefactual.

Electromyography

It was agreed that measurement of fibre density or motor unit potential duration is the only objective assessment of denervation. These measurements should be combined with a method which assesses conduction defects. Measurement of pudendal nerve terminal motor latency seems to be the most widely recognized and reproducible technique for detecting conduction defects in the terminal portion of the pudendal nerve. The pudendoanal reflex is subject to synaptic delay and is not recommended for use. The anocutaneous reflex is associated with three responses, the early responses being due to short-circuiting, hence the reflex is no longer used for detecting conduction defects in the pudendal nerve.

Electromyography is useful for mapping a deficient or ectopic sphincter. The technique is also useful for defining 'anismus'.

Fine wire electrodes are ideal for monitoring electrical activity in the puborectalis, external sphincter and even the internal sphincter, during functional studies of pelvic floor activity.

Proctography

It was agreed that proctography should be performed in the seated position on a water-filled apparatus to obtain lateral projections of the pelvis and perineum. It is desirable to mark the symphysis pubis and the perineal skin as well as the anal canal and the vagina with radio-opaque markers. Video monitor linkage is essential so as to analyse activity from frozen frames taken at rest, during maximal pelvic floor contraction and during attempted defaecation. A thick barium suspension should be used by emulsifying contrast material with cellulose and a known weight and volume should be introduced into the rectum.

Videoproctography provides a means of assessing the speed of evacuation and recordings may be combined with internal and external sphincter EMG and puborectalis EMG as well as anal and rectal manometry.

Anorectal angles may be assessed using the centroid of the rectum such that a line drawn from the centroid to the anorectal junction divides the rectum into two equal areas. Conventional measurement of anorectal angle using the posterior border of the rectum is difficult to define because this line may not be straight particularly during pelvic floor contraction. On the other hand, use of the posterior margin of the rectum is the method that has been used most extensively in the literature and the one that is likely to be adopted in the future. Other parameters which can be measured in relation to the

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For a list of contributors see the Appendix to this paper.

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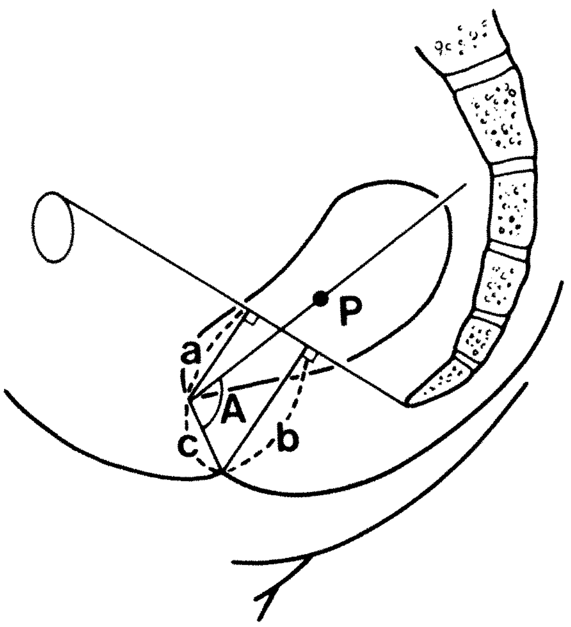

Figure 1 *Anatomical measurement in proctogram. A, anorectal angle; a, pelvic floor descent; b, perineal descent; c, anal canal length; P, centroid. This Figure is reproduced from Yoshioka* et al.[1]

pubococcygeal line and which have predictive function include: pelvic floor descent, perineal descent and anal canal length (*Figure 1*).

There is a need for clear definitions, particularly of abnormalities such as infoldings, rectal and anal intussusception, rectocele, and megarectum as some of these visual abnormalities occur in normal subjects.

The Lahr balloon which was introduced into office practice in North America, is unreliable and should be abandoned.

Isotopic rectal emptying

Isotopic estimation of rectal emptying allows the construction of a time course for evacuation using γ camera images from the pelvis. ^{99}Tc aluminium/magnesium silicate gel provides a useful method of introducing an isotope into a semisolid material having a consistency similar to that of faeces. If this material is introduced into the sigmoid colon an assessment can be made of rectal filling as well as rectal emptying.

Colonic transit studies

It was agreed that the most objective assessment of colonic transit is obtained by asking patients to take three different types of radio-opaque markers each morning for 3 days while they are fully ambulatory and receiving no laxatives. A plain radiograph of the abdomen is obtained on the 4th and 7th day. The abdomen is divided into three areas of interest: the right colon, the left colon, and the rectum and sigmoid area. Mean colonic transit (MCT) can be determined using the formula: $MCT = 1{\cdot}2\ (N_1 + N_2 + N_3)$ where N_1 is the number of the first type of marker, N_2 the number of the second type of marker and N_3 the number of the third type of marker[2].

Colonic motility studies

Colonic motility recordings are difficult to interpret; where possible they should be performed on the unprepared colon using multichannel infusion techniques. The data should be digitized and stored on computer. There will be advantages in the future if studies of colonic motility can be combined with an isotopic assessment of rectosigmoid propulsive activity.

Anal sensation

Assessment of anal sensation is largely a research tool. Mucosal electrosensitivity is the most widely measured parameter and provides an objective assessment of denervation involving the afferent side of the reflex arc of the pudendal nerve[3]. Mucosal electrosensitivity may be measured using bipolar or monopolar electrodes. The technique should be stated.

Rectoanal inhibitory reflex

The rectoanal inhibitory reflex must be assessed at sites throughout the anal canal as it may not be apparent when recordings are made near the anal verge. The reflex is absent after low rectal excision and is normally absent in Hirschsprung's disease. The reflex may also be absent if resting anal canal pressures are low, as in some patients with rectal prolapse for neurogenic faecal incontinence. The response depends on the volume, consistency and speed of rectal filling. The volume required to inhibit recovery of the reduction in resting anal pressure should also be recorded.

It was agreed that a positive response could be defined as any reduction in resting anal pressure after inflation of air into a rectal balloon. The threshold volume needed to elicit the response should be recorded as well as the duration of the reflex.

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Appendix

Contributors: *UK*. A. Allan (Birmingham), D. C. C. Bartolo (Bristol), N. R. Binnie (Edinburgh), I. Finlay (Glasgow), M.M.Henry (London), M. R. B. Keighley (Birmingham), R.H.S.Lane (Winchester), R. Miller (Bristol), N. J. McC. Mortensen (Oxford), J. Nicholls (London), M. Pinho (Birmingham), N. Read (Sheffield), A. Roe (Bristol), J. Rogers (London), A. Smith (Edinburgh), N. S. Williams (London) and N. Womak (London). *Overseas*. J. Coller (Boston, USA), J.Fleshman (St. Louis, USA), H. Kuijpers (Nijmegen, The Netherlands), D. Lobowski (Sydney, Australia), P. Mahieu (Brussels, Belgium), J. Pemberton (Rochester, USA), F. Penninckx (Brussels, Belgium), J. Varma (Hong Kong/Edinburgh) and D. Wong (Minneapolis, USA).

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Localization of lower gastrointestinal bleeding using in vivo technetium-99m-labelled red blood cell scintigraphy

M. L. Nicholson, J. P. Neoptolemos*, J. F. Sharp, E. M. Watkin†, and D. P. Fossard

Department of Surgery, Leicester Royal Infirmary, and †Department of Radiology, Leicester General Hospital, Leicester, UK

Correspondence to:
Mr M. L. Nicholson, Department of Surgery, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, UK

Technetium-99m-labelled red blood cell scintigraphy was used in the investigation of 41 patients with major rectal haemorrhage. Red cells were labelled in vivo *with technetium-99m pertechnetate and serial scans (0–36 h) were taken using a large field γ camera. Twenty-two men and 15 women, mean age 71·3 years (range 32–91 years), and four children were studied. Forty-three scans were performed in all and there were 31 positive and 12 negative results. In each case the accuracy of the scan in localizing the bleeding site was checked either by independent investigations or at laparotomy. A definite bleeding site was identified in 30 cases and red cell scintigraphy correctly localized 29 of these (sensitivity 97 per cent). In the remaining 13 cases a bleeding site was not identified by any of the independent investigations and in this group there were two false positive scans (specificity 85 per cent). The investigation had a high predictive value when both positive (94 per cent) and negative (92 per cent). These data suggest that technetium-99m-labelled red cell scintigraphy should be used more widely in the investigation of patients with suspected lower gastrointestinal haemorrhage.*

Keywords: Intestinal haemorrhage, investigation, scintigraphy

The preoperative localization of the bleeding site in patients presenting with lower gastrointestinal haemorrhage remains a difficult clinical problem. Conventional barium studies fail to isolate a potential bleeding site in 20–30 per cent of cases[1] and, even if a lesion is identified, there is no certainty that it is the source of haemorrhage. Colonoscopy can be diagnostic, but profuse haemorrhage usually makes it impractical by obscuring the view. Selective angiography is invasive and only yields a positive result when bleeding is occurring at the time of contrast injection and at a rate $>0{\cdot}5$–$1{\cdot}0\,\mathrm{ml/min}$[2,3].

Radionuclide methods for diagnosing the site of gastrointestinal bleeding have now been available for over 10 years but have not been favoured in this country and were not mentioned in a recent leading article in the *British Medical Journal*[4]. The isotope of choice has invariably been technetium-99m and this has been used to label sulphur colloid[5], albumin[6], diethylene triamine penta-acetic acid (DTPA)[7] and red blood cells[8]. In this paper we report our experience of *in vivo* labelled red blood cell scintigraphy in the investigation of suspected lower gastrointestinal bleeding.

Patients and methods

Patients presenting with major rectal haemorrhage over the 3-year period June 1984–May 1987 were studied. The investigation of the source of haemorrhage in all cases included *in vivo* technetium-99m-labelled red cell scintigraphy. Major rectal haemorrhage was defined as a transfusion requirement of three or more units of blood or an acute fall in haemoglobin level $\geq 20\,\mathrm{g/l}$.

Red cells were labelled *in vivo* by intravenous injection of 1·7 mg stannous chloride and 12 mg sodium pyrophosphate in 2 ml sterile saline, followed 20 min later by technetium-99m pertechnetate in a dose appropriate to the patient's body-weight (range 395–600 MBq)[9]. The stannous pyrophosphate generated binds to red blood cells and then combines with technetium-99m pertechnetate to give labelled red cells. A large field γ camera (Siemens ZLC 370S, Siemens Ltd., Sunbury, UK) with C stand and low energy all purpose parallel collimator was used to perform serial scans, (using 1×10^6 counts per view) starting immediately after isotope injection and continuing at 10-min intervals up to 1 h. If these early images were negative, delayed scans were performed at variable times up to 36 h after isotope injection. Standard anteroposterior views were obtained in all cases, but, where indicated, oblique and lateral views were used to separate possible sites of abnormal activity from background activity in the liver, spleen, kidneys, bladder and great vessels. The investigation was considered to be positive if focal areas of abnormal activity were seen to develop on serial scans (*Figures 1–3*). Negative scans were those which only demonstrated background activity (*Figure 4*).

The sites of bleeding indicated by scintigraphy were compared with the findings of other investigations, including barium studies, colonoscopy and selective mesenteric arteriography, and the findings at laparotomy if performed. In the positive-scan group, the time interval between the injection of isotope and the development of a positive result was recorded for individual scans. The blood transfusion requirements in the 24 h before scanning were recorded and the findings correlated with the scan result. The day after admission on which each scan was performed was also noted.

The accuracy of the isotope scans in localizing bleeding sites was expressed as sensitivity, specificity and predictive values. Statistical analysis was performed using the Mann–Whitney U test for continuous variables and the χ^2 test for discrete variables.

Results

Forty-one patients were studied but as two of these suffered two separate bleeding episodes a total of 43 scans was performed. There were 22 men and 15 women with a mean age of 71·3 years (range 32–91 years) and four children (range 5 months–12 years). The mean haemoglobin concentration at presentation was 9·4 g/dl (range 5·4–13·5 g/dl) and the mean blood volume transfused was 8·2 units (range 3–20 units). Corroborative evidence of the bleeding site was obtained from independent investigations whenever possible. Laparotomy was required in 15 cases and on-table colonoscopy was also used in three of these. The results of routine histological examination of resected bowel were taken into account when deciding the final diagnosis in these cases. In eight patients a

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* *Currently Senior Lecturer in Surgery, Dudley Road Hospital, Birmingham, UK.*

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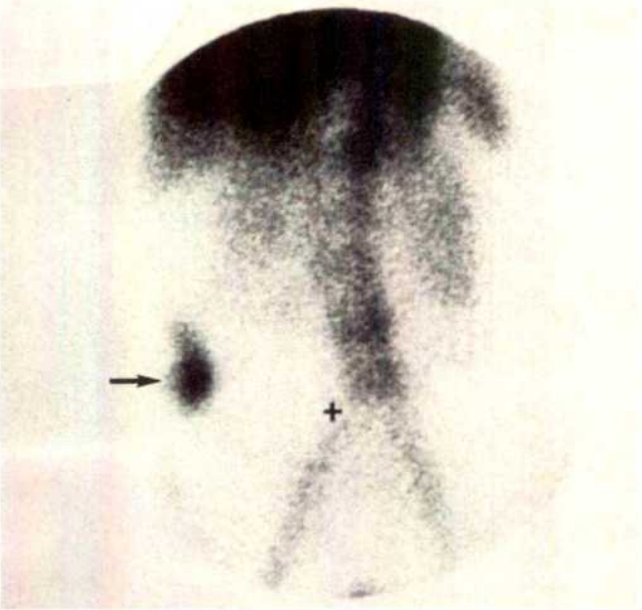

Figure 1 *Scintigraphic scan showing abnormal activity (arrowed) in the caecum 20 min after isotope injection. This patient underwent a right hemicolectomy for bleeding from caecal angiodysplasia*

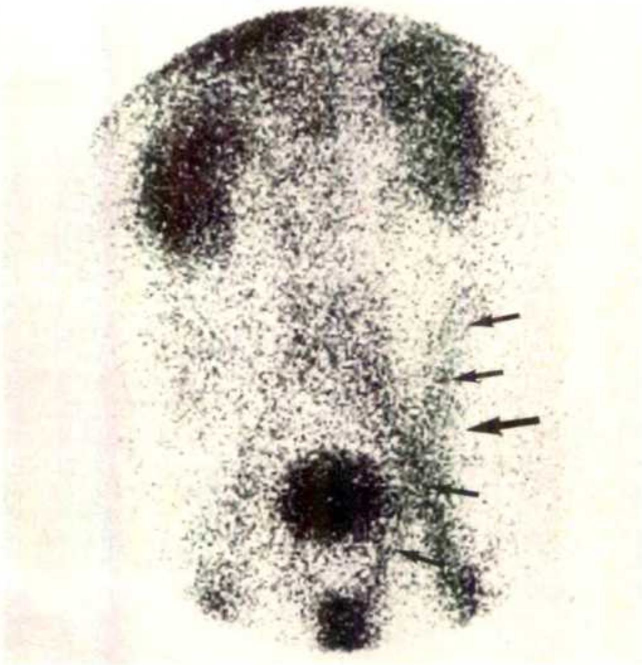

Figure 2 *A delayed scan (28 h) showing labelled blood in the descending and sigmoid colon in a case of bleeding from an area of diverticular disease*

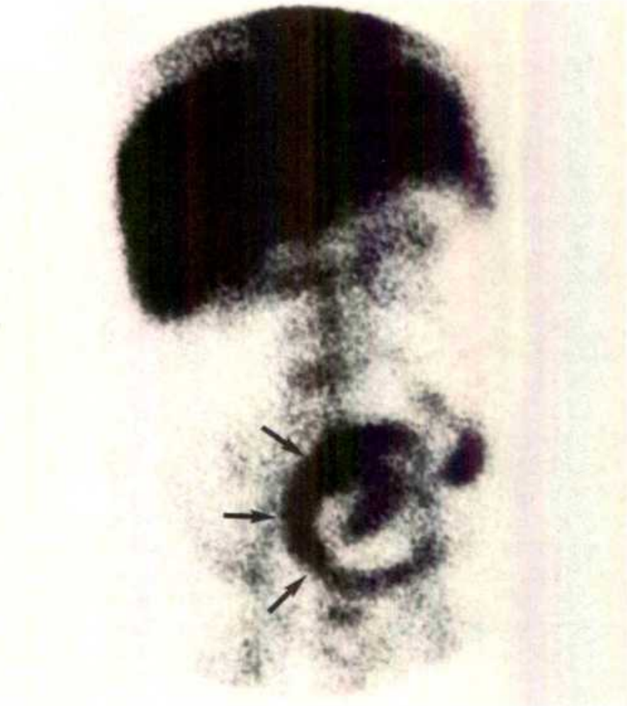

Figure 3 *Forty-minute image of a scintigraphic scan showing extravasated radiolabelled blood in a loop of small bowel which was extremely ischaemic, requiring resection*

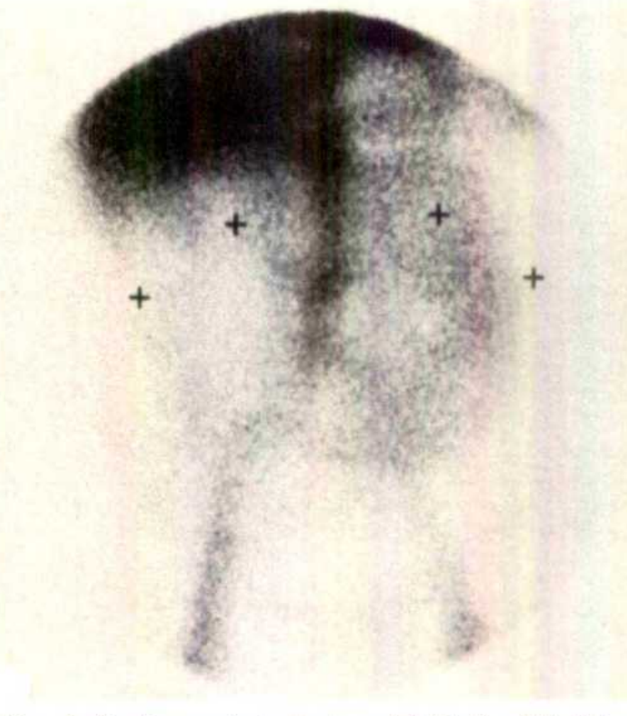

Figure 4 *Baseline scan showing background distribution of labelled red cells for comparison*

lesion was visualized on barium studies, but in each case at least one further investigation was used to confirm that the lesion seen was the source of haemorrhage. In 11 cases the final diagnosis was made at colonoscopy, selective angiography was diagnostic in a further three cases and in one patient the bleeding point was identified at post-mortem examination.

In 30 cases a definite bleeding site was identified. The following diagnoses were made: diverticular disease in 15, angiodysplasia in ten, Meckel's diverticulum in two, small bowel ischaemia in two and recurrent colon cancer at an anastomosis in one case. In the 11 remaining patients no definite bleeding site was established by the investigations used.

Thirty-one scans were positive and in 29 of these the site of haemorrhage demonstrated on scanning was confirmed as correct by independent methods. In the remaining two cases with positive scans, no bleeding point was identified by the other investigations employed and so these scans were taken to be false positive results. Both cases were managed successfully by conservative measures. The remaining 12 scans were negative. However, in one of these patients a bleeding angiodysplastic lesion was seen at colonoscopy and it was successfully treated by diathermy coagulation. This was the only proven false negative result in the series. In the other 11 cases with negative scans no bleeding point was identified by other investigations and the scans were taken to be true negative results. By using the findings of the independent methods of investigation as the standard, *in vivo* technetium-99m-labelled red cell scintigraphy had a sensitivity of 97 per cent and a specificity of 85 per cent. The predictive value of a scan when positive was 94 per cent and when negative was 92 per cent.

Within the group of patients who had a positive and corroborated scan, 15 underwent an operative procedure: right hemicolectomy in five, left hemicolectomy in two, sigmoid colectomy in three, subtotal colectomy in one, laparotomy and biopsy of a recurrent colonic neoplasm in one, small bowel resection in one and Meckel's diverticulectomy in two. Of the other 14 patients with a positive corroborated scan, 13 were managed conservatively and the other, a 5-month-old child with multiple congenital abnormalities, died from massive haemorrhage before surgery.

All of the 11 patients in whom no definite bleeding site could be identified were managed successfully by conservative measures alone. This group was followed for a minimum of 3 months and bleeding did not occur.

The time intervals between the injection of isotope and the development of a positive scan varied considerably (*Figure 5*). Approximately 30 per cent of the 31 positive scans showed a result in the first hour after injection and a further nine became positive between 1 and 6 h. However, a significant number of positive results only developed between 12 and 36 h after injection. As the transfusion rate in the previous 24 h increased, the probability of a scan showing a positive result also increased (*Table 1*).

Figure 6 shows the relationship between the scan result and the time after admission that the scan was performed. Positive scans fell into two distinct groups: those performed in the first 4 days after admission and those performed later during the second week. This latter group represents patients who rebled in hospital. The negative scans did not conform to any particular pattern. In general, positive scans were performed earlier (median 3 days) than negative scans (median 5·5 days), but this difference did not reach statistical significance ($P = 0{\cdot}132$; Mann–Whitney U test).

Table 1 *Transfusion requirements in the previous 24 h and technetium-99m red cell scan results*

Blood replacement in the previous 24 h (units)	Positive scans	Negative scans
≤1	5	5
2	9	6
≥3	17	1

$\chi^2 = 7{\cdot}99$, 2 degrees of freedom $P < 0{\cdot}02$

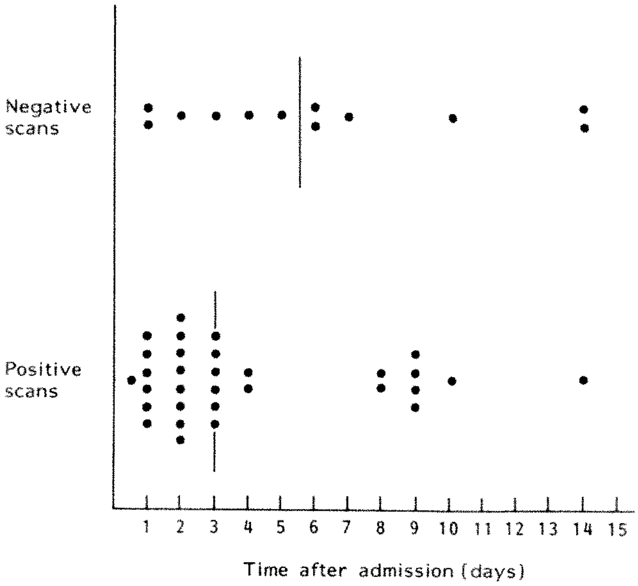

Figure 6 *The relationship between scan result and the time after admission that the scan was performed. Vertical bars show median times after admission*

Discussion

Localization of the bleeding point remains a difficult clinical problem in the management of patients presenting with major lower gastrointestinal haemorrhage. Two types of lesion which may frustrate even the most thorough investigation are those which bleed slowly and those which bleed intermittently. Successful angiography requires a bleeding rate of 0·5–1·0 ml/min (References 2 and 3) and an important limitation of the technique is that it will only give positive results if active bleeding is occuring at the time of contrast injection. Scintigraphy can detect even lower rates of 0·05–0·1 ml/min[10], but, more importantly, when labelled red cells are used, their long intravascular half-life allows repeated scanning to be performed over 36 h, without injection of further isotope. This greatly increases the probability of isolating a lesion which is bleeding intermittently. Although comparisons between angiography and scintigraphy are inevitable, the two techniques can be complementary and it has been suggested that angiography can be more rationally employed after a positive radionuclide scan has orientated this to the appropriate vessel[2,11].

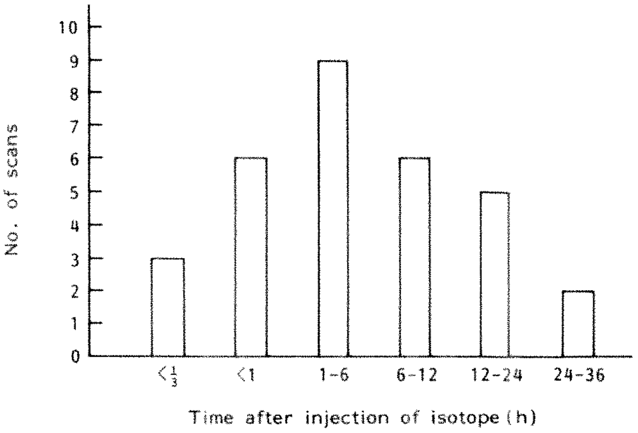

Figure 5 *Positive scans: the time interval from injection of isotope to development of positive result*

Many different isotopic methods have been used for the detection of gastrointestinal haemorrhage. Technetium-99m-sulphur-colloid[5] and technetium-99m-DTPA (diethylene-triamine penta-acetic acid) scanning have the disadvantage, like angiography, that bleeding must be occurring at the time of injection. This is because these radionuclides have a short intravascular half-life, being rapidly cleared by the liver, spleen or kidneys. Furthermore, background counts which appear in the organs that clear these tracers may mask the bleeding point being sought. Technetium-99m-labelled albumin[6] and red cell scans are based on a different principle. These tracers are retained in the circulation, accumulating at a bleeding site and gradually becoming detectable over a period.

Although there are several reports of the successful use of labelled red cell scans in the North American literature[1,8,11–13] the technique has not been reported extensively in the UK. In contrast to our results, false negative rates of 40–50 per cent have been reported[14] and this may be a factor. In our series there were 11 patients with negative scans in whom no bleeding point could be identified by the other investigations performed. By using these independent investigations as the standard against which the accuracy of scintigraphy is calculated, these 11 scans were defined as true negative results. However, it is clear that these patients all had a clinically significant lower gastrointestinal haemorrhage and we accept that the false negative rate may be higher than calculated here. Selective angiography was used very little in our patients but a recent small series did demonstrate technetium-99m red cell scanning to be more sensitive than angiography in localizing bleeding lesions[15]. The procedure is simple and non-invasive and this makes it particularly suitable for critically ill patients.

Red cell scintigraphy can only localize bleeding sites approximately, but we have found that the ability of the method to differentiate between haemorrhage coming from the small rather than the large bowel or from one side of the colon rather than the other was enough to plan surgery logically. This is a major advantage of the investigation because in the past when the cause of colonic bleeding could not be isolated at surgery, the procedure of choice was subtotal colectomy. This operation carries an operative mortality rate of up to 11 per cent[16] and should be avoided if possible.

It is not always clear on purely clinical grounds exactly when a bleeding episode starts and stops and this may cause difficulties in deciding the timing of scanning. However, when three or more units of blood were given in the 24 h before scanning, the ratio of positive to negative scans was very high and so transfusion requirements are a helpful guide. The timing of repeated scans must also be carefully judged because isotope in the gut will move caudally between repeat scans and this could lead to false localization. This problem can be countered to some extent by performing repeated scans at 10–min intervals after any scan which is suspicious of bleeding. In this way bleeding sites can be seen to be developing and the caudal movement on subsequent scans actually becomes a helpful feature in distinguishing a true area of abnormal activity from background activity.

In this study, red cell scintigraphy was successful in identifying bleeding from colonic angiodysplasia. These lesions are so common that they are often seen incidentally at colonoscopy or arteriography, causing considerable confusion when a second lesion is the actual source of bleeding[17].

This study demonstrates that the technique of *in vivo* technetium-99m-labelled red cell scintigraphy is both sensitive and specific in the localization of lower gastrointestinal haemorrhage. Our data suggest that this investigation deserves a more prominent place in the management of lower gastrointestinal bleeding.

Acknowledgements

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Colonic complications of severe acute pancreatitis

Colonic complications are rare in acute pancreatitis. Over the last 9 years at St. Mary's Hospital, London, UK, we have managed severe acute pancreatitis by intensive supportive therapy followed by sub-total pancreatic resection and/or debridement in those who fail to improve. Of the 22 patients who have undergone this form of surgery, nine were found to have colonic involvement in the form of either necrosis or perforation. In addition, one patient presenting at West Middlesex University Hospital, Isleworth, UK, had severe acute pancreatitis and almost total colonic necrosis as an unexpected finding at emergency laparotomy. These ten patients comprised seven men and three women of median age 59 years and with a median of four Ranson criteria. In seven patients, colonic involvement was discovered at the time of pancreatic surgery or laparotomy for pancreatitis and in the remainder it presented between 1 and 3 weeks later as either a faecal fistula (n = *2) or persistent abdominal sepsis* (n = *1). The ascending colon was involved in one patient, the splenic flexure and descending colon in one, the transverse colon in three, the splenic flexure alone in four, and one patient had almost total colonic involvement. All patients underwent resection of the involved colon and exteriorization with either a proximal colostomy* (n = *7) or ileostomy* (n = *3) and a distal mucous fistula. Pathological examination of the resected colons revealed a spectrum of changes from pericolitis through to ischaemic necrosis suggesting at least two possible mechanisms. Six patients died from overwhelming sepsis between 1 day and 4 weeks (median 11 days) after colonic resection. Severe acute pancreatitis must be recognized as a cause of colonic ischaemia and necrosis; this complication is associated with a very poor prognosis despite surgical intervention.*

Keywords: Pancreatitis, pancreatic necrosis, colonic necrosis, colonic perforation, ischaemic colitis

M. C. Aldridge,
N. D. Francis*, G. Glazer
and H. A. F. Dudley

Academic Surgical Unit and
**Department of Histopathology,*
St. Mary's Hospital, London W2 1NY
UK

Correspondence to:
Mr M. C. Aldridge, Unite de
Chirurgie Hépato-Biliaire, Hôpital
Paul Brousse, 94800 Villejuif,
France

Colonic involvement is an uncommon but potentially lethal complication of severe acute pancreatitis which has received little attention in the UK surgical literature. It has been estimated that 1 per cent of patients with acute pancreatitis develop a colonic complication[1]. The spectrum of colonic involvement includes: localized ileus which can be seen as the so-called 'colon cut-off' sign[2,3] on a plain abdominal film; mechanical obstruction from either extrinsic compression by a pancreatic inflammatory mass or an intrinsic post-pancreatitic colonic stenosis; fistula formation; and colonic necrosis.

In this paper we report our experiences at St. Mary's Hospital, Isleworth and West Middlesex University Hospital, London, UK, in the mangement of ten patients with severe acute pancreatitis who developed serious colonic complications, namely necrosis and perforation.

Patients and methods

At St. Mary's Hospital during the 9-year period from 1979 to 1987, 22 patients with severe acute pancreatitis have been managed by intensive supportive therapy followed by either sub-total pancreatic resection ($n = 19$) or peripancreatic debridement ($n = 3$). Our experiences in the management of the first 15 of these patients have been reported previously[4]. Of these 22 patients, nine had involvement of the colon to such a degree that the bowel was considered non-viable by the operating surgeon and was resected. In addition, one patient is reported from West Middlesex University Hospital who was found to have severe acute pancreatitis and almost total colonic necrosis at emergency laparotomy for peritonitis. These ten patients form the basis of this report and their clinical features and outcome are summarized in *Table 1*.

Sex and age

There were seven men and three women with ages ranging between 26 and 72 years. The median age of the men in the series was 58 years and that of the women 62 years. The overall median age was 59 years.

Aetiology and severity of pancreatitis

High alcohol intake was thought to be the cause of pancreatitis in six of the ten patients (60 per cent). In addition, two of these patients also had gallstones. Gallstones were the single aetiological factor in two patients. In one man there was no obvious cause for his attack of pancreatitis and one woman developed postoperative pancreatitis following open cardiac surgery and cardiac bypass. All ten patients had severe acute pancreatitis with three or more Ranson criteria[5], the median for the group being four (range from three to seven). Four patients were referred to St. Mary's Hospital from other hospitals because of difficulties in the management of their attack.

Timing and extent of pancreatic surgery (Table 1)

Two forms of presentation leading to surgery were seen—early and late—as previously described[4]. Four patients were admitted with fulminant necrotizing pancreatitis and deteriorated rapidly despite intensive care support including ventilation. In these patients, the interval between onset of acute pancreatitis and pancreatic surgery was 2 days, 4 days (two patients) and 14 days. In five patients, pancreatic surgery was carried out between 2 and 8 weeks after the onset of the attack. Two of these five patients had undergone surgery before their pancreatic resection. Patient 6 had had an attempted cystgastrostomy for what was thought to be a pseudocyst but which in reality was pancreatic necrosis and Patient 8 had undergone a cholecystectomy and exploration of the common bile duct for gallstone-associated pancreatitis. In neither case were rigid drains used which could have caused the colonic damage.

Six patients with pancreatic necrosis underwent sub-total pancreatic resection with removal of the body and tail of the gland[4]. Two patients, also with gland necrosis, had necrosectomy and one patient with a pancreatic abscess and necrosis underwent drainage of the abscess and distal pancreatectomy.

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Table 1 *The timing and extent of pancreatic and colonic surgery in ten patients with severe acute pancreatitis who developed colonic complications.*

Patient	Age and sex		Ranson criteria (Ref. 5)	Aetiology	Pancreatic lesion	Pancreatic surgery	Site of colonic involvement	Colonic surgery	Outcome	Hospital stay (days)
1	26	M	6	Alcohol	Necrosis	Sub-total resection (day 2)	Splenic flexure	Resection with proximal colostomy + mucous fistula (day 21)	Died (day 23)	
2	32	M	3	Alcohol	Necrosis	Sub-total resection (day 4)	Splenic flexure	Resection with proximal colostomy + mucous fistula (day 18)	Survived	192
3	33	F	7	Gallstones	Necrosis	Necrosectomy (day 14)	Ascending colon	Right hemicolectomy (day 18)	Died (day 19)	
4	55	M	4	Alcohol	Necrosis	Sub-total resection (day 30)	Transverse colon	Resection with proximal colostomy + mucous fistula (day 30)	Survived	88
5	58	M	3	Idiopathic	Abscess	Drainage of abscess + distal pancreatectomy (day 16)	Transverse colon	Extended right hemicolectomy (day 16)	Survived	80
6	60	M	3	Alcohol	Necrosis	Necrosectomy (day 56)	Splenic flexure	Resection with proximal colostomy + mucous fistula (day 56)	Died (day 86)	
7	62	F	4	Post-operative	Necrosis	Sub-total resection (day 21)	Splenic flexure	Resection with proximal colostomy + mucous fistula (day 21)	Died (day 27)	
8	64	F	5	Gallstones	Necrosis	Sub-total resection (day 30)	Splenic flexure, descending colon	Resection with proximal colostomy + mucous fistula (day 30)	Survived	241
9	67	M	6	Gallstones + alcohol	Necrosis	Sub-total resection (day 4)	Transverse colon	Resection with proximal colostomy + mucous fistula (day 4)	Died (day 21)	
10	75	M	5	Gallstones + alcohol	Necrosis	—	Transverse colon, splenic flexure, descending colon	Sub-total colectomy (day 1)	Died (day 29)	

Day 1 = day of admission. The timing of surgery is shown in parentheses

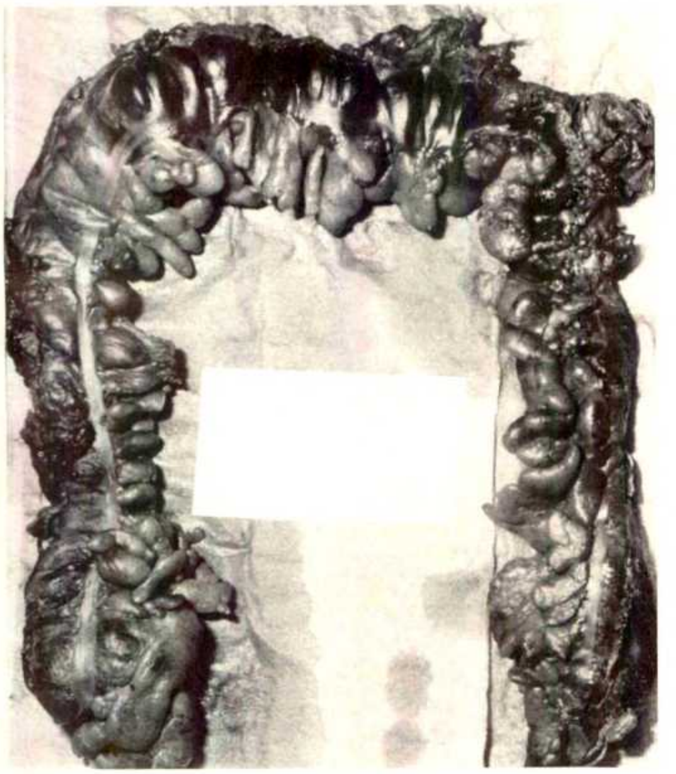

Figure 1 *Patient 10. At laparotomy this patient was found to have severe acute pancreatitis and infarction of the transverse colon, splenic flexure and descending colon. The abrupt demarcation between normal and infarcted colon is clearly seen in the region of the hepatic flexure*

Patient 10 did not undergo pancreatic surgery. This elderly man underwent emergency laparotomy for peritonitis at West Middlesex University Hospital. Severe haemorrhagic pancreatitis with infarction to the transverse colon, splenic flexure and descending colon (*Figure 1*) were unexpected findings. He underwent sub-total colectomy with formation of an ileostomy and distal mucous fistula and drains were inserted. Five days postoperatively he had a cerebrovascular accident which precluded further surgery.

Timing and extent of colonic surgery (Table 1)

In seven patients, colonic involvement was present at the time of pancreatic surgery or diagnostic laparotomy (Patient 10) but in three it presented between 4 and 19 days postoperatively. The indications for further surgery in these three patients were persistent abdominal sepsis in one and the appearance of faecal fluid from drains in the left upper quadrant in two.

In nine patients, the consultant surgeon in-charge (G.G. or H.A.F.D.) considered the colon to be non-viable and that resection was indicated (four patients having perforations at the splenic flexure). Patient 10 was operated on by M.C.A. while he was a senior registrar at West Middlesex University Hospital. At St. Mary's Hospital, operations were performed by the consultant in-charge (G.G. or H.A.F.D.) or by senior registrars under the guidance of one or other consultant.

The transverse colon alone was involved in three patients, the splenic flexure alone in four patients, the splenic flexure and descending colon in one patient, the ascending colon in one patient and almost the whole colon in one patient. All patients underwent colonic resection with the formation of either a proximal colostomy ($n = 7$) or ileostomy ($n = 3$) and distal mucous fistula.

Results

Colonic histology (Table 2)

In four patients the resected colon showed evidence of ischaemic

Table 2 *Colonic histology. A diagnosis of either 'pericolitis' or 'ischaemic necrosis' is given for each patient*

Patient	Site of vascular thrombosis	Evidence of ischaemia	Perforation	Serosa	Fat necrosis	Conclusion
1	—	—	+ (diverticulum)	Fibrosis, granulation tissue and acute peritonitis	—	Perforation of congenital diverticulum ? due to pericolic inflammation
2	—	Haemorrhage + congestion adjacent to perforation	+	Fibrosis and congestion with granulation tissue along perforation track	+	Pericolitis and secondary perforation
3	Small serosal vessels	A few inflammatory cells in the mucosa	—	Peritonitis, haemorrhage and granulation tissue	+ +	Mild ischaemic changes with serosal thrombi in an area of pericolitis
4	—	A few inflammatory cells in the mucosa	—	Fibrosis and congestion	+	Pericolitis and mild mucosal ischaemic changes
5	Mesentery (+ +)	Mucosal ischaemic changes and congested submucosa	—	Granulation tissue	+	Ischaemic necrosis
6	—	Haemorrhage + congestion adjacent to perforation	+	Congestion and granulation tissue along perforation track	+	Pericolitis
7	—	Early mucosal ischaemia and congested submucosa	—	Normal	—	Early ischaemic colitis
8	—	—	+ (diverticulum)	Acute inflammation and fibrous organization of granulation tissue	+	Perforated acquired diverticulum ? due to pericolic inflammation
9	Submucosa (+ +)	Full-thickness mucosal infarction	—	Fibrosis, congestion and granulation tissue	+ +	Ischaemic necrosis
10	Mesentery submucosa pericolic fat	Full-thickness mucosal infarction	—	Congestion + inflammation	+ +	Ischaemic necrosis

+, Present; + +, marked

damage (Patients 5, 7, 9 and 10). This ranged from very early superficial mucosal necrosis, epithelial cell sloughing, oedema and congestion of the lamina propria to full-thickness infarction (*Figure 2*). In the latter case (Patient 9) large submucosal vascular thrombi were seen in association with the infarcted area (*Figure 2*). In two cases, large vascular thrombi were also present in the mesentery and in this group areas of macroscopic 'fat necrosis' were in fact dead or infarcted fat as would be expected with a primary vascular cause. In these four cases, colonic necrosis most probably developed from inside to outside.

In six patients there was no evidence of mucosal or submucosal ischaemic damage in the resected colon, all changes being confined to the external layers of the colonic wall (Patients 1, 2, 3, 4, 6 and 8). In four patients (Patients 1, 2, 6 and 8) the colon contained a perforation which in two was through a diverticulum—congenital (in view of his age) in Patient 1 and acquired in Patient 8. In both there was serosal inflammation and organized peritonitis suggesting that the external inflammation secondary to acute pancreatitis may have precipitated the perforation. In neither case was there evidence of a primary diverticulitis. In the remaining two cases (Patients 2 and 6) there were abrupt changes at the mucosal surface from almost normal mucosa to the congested granulation tissue of the margin of the perforation track (*Figure 3*). In both specimens there was marked organization and fibrosis of the wall of the track extending to the serosal surface.

In two cases (Patients 3 and 4) the primary colonic damage was at the serosal surface and in the mesenteric/pericolic fat where fat necrosis, peritonitis, congestion, haemorrhage and some organization were seen. In Patient 4 there was evidence of ischaemic mucosal damage. In these six patients therefore, there was most likely spread of peripancreatic necrosis to involve the colonic wall from outside to inside.

Mortality

Six patients died between 1 and 30 days after colonic resection. The cause of death was overwhelming sepsis and multi-organ failure in five and massive retroperitoneal haemorrhage in one. In addition to sepsis and organ failure, Patient 10 also suffered a cerebrovascular accident which contributed to his death. Almost total necrosis of the pancreas was found at post mortem.

Of the four survivors, three have undergone successful colonic re-anastomosis and one (Patient 8) has refused further surgery and returned to her country of origin. The length of hospital stay in days for the four surviving patients (Patients 2, 4, 5 and 8) was 192, 88, 80 and 241 respectively.

Discussion

Colonic complications are believed to be rare in acute pancreatitis but the exact frequency is unknown. Twenty years ago Lukash[1] reviewed 100 patients with acute pancreatitis and found only one with a colonic lesion—an area of stenosis at the hepatic flexure on barium enema. Subsequently a number of authors have quoted an incidence of 1 per cent for this complication but clearly a larger sample size is required before the exact incidence can be determined.

The spectrum of colonic involvement in acute pancreatitis is broad. The commonest manifestation is probably colonic ileus which is seen on a plain abdominal X-ray as the 'colon cut-off sign' described by both Stuart[2] and Price[3]. It usually affects the splenic flexure and its incidence has been reported as between 1 and 14 per cent of all cases of pancreatitis[6–9]. The exact cause is unknown but it may be a visceral reflex mediated by the superior mesenteric plexus in the presence of retroperitoneal inflammation and/or transient colonic ischaemia[10].

The more serious forms of colonic involvement are: obstruction, necrosis, perforation and fistula formation. Colonic obstruction may occur from either extrinsic

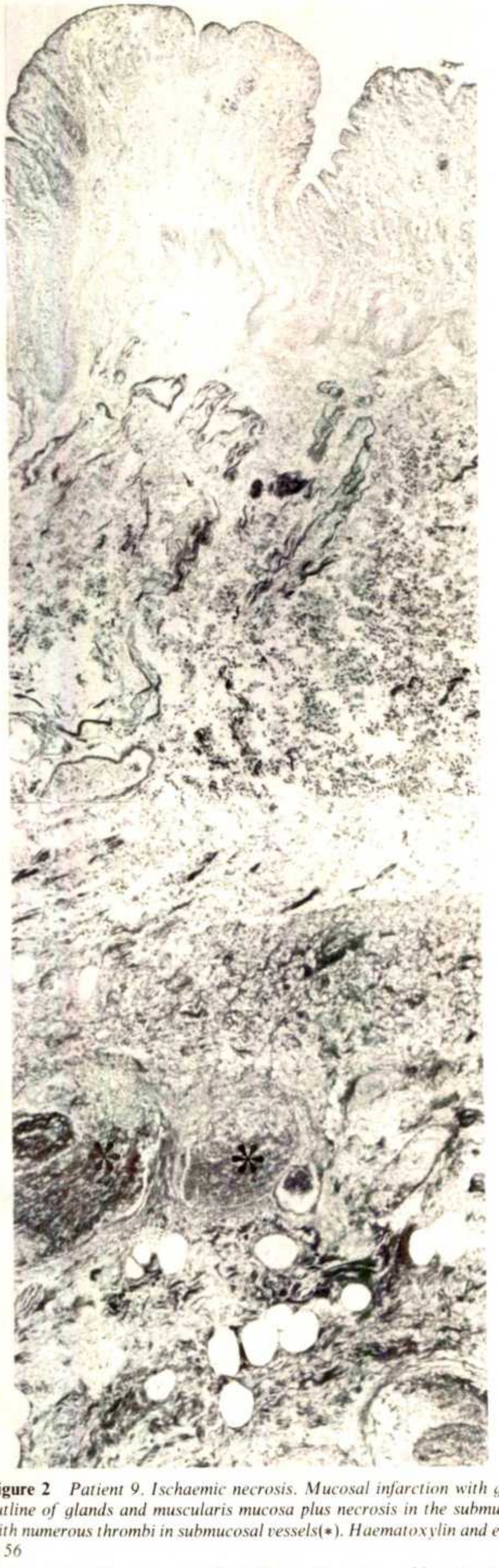

Figure 2 *Patient 9. Ischaemic necrosis. Mucosal infarction with ghost outline of glands and muscularis mucosa plus necrosis in the submucosa with numerous thrombi in submucosal vessels(*). Haematoxylin and eosin, ×56*

compression by a pancreatic inflammatory mass[11] or pericolic fibrosis. Colonic stenosis may present as large bowel obstruction during an attack of acute pancreatitis or some months later as a 'pseudocarcinoma' with rectal bleeding and an 'apple-core' lesion seen on barium enema. Seventy-eight cases have been reported in the world literature and in reviewing these Carboni and colleagues[10] noted that the site of stenosis was at the splenic flexure in 84 per cent. This area of the colon is at the watershed between the areas of supply of the middle and left colic arteries[12] and is often supplied by a poorly developed marginal artery[13]—facts which might suggest an ischaemic cause especially during periods of hypotension as occur in severe acute pancreatitis[14]. The splenic flexure, however, is also in close proximity to the tail of the pancreas and thus direct spread of enzyme-rich fluid, fat necrosis and peripancreatic inflammation to involve the colon may also be a significant causative factor[15].

The first report of colonic involvement in acute pancreatitis came from the USA in 1945 when Morton[16] described two patients, one with a pancreatic abscess and one with haemorrhagic pancreatitis, who both developed fistulae into the transverse colon and who both died from massive haemorrhage. In the same year, Moore and Castleman[17] reported a patient with pancreatitis who developed colonic infarction and inferior mesenteric vein thrombosis and died 63 h after the onset of symptoms.

In the past 22 years there have only been 36 cases of colonic necrosis and/or perforation reported in the world literature and our present account of ten patients now represents one of the largest series from a single centre. The frequency of this complication in our patients appears high. There may be several reasons for this. Firstly, we were operating on the most critically ill patients with severe acute pancreatitis—patients who were deteriorating and who, in many cases, were referred from other centres. In the past these patients may have been considered unsalvageable and would have died from abdominal sepsis with their colonic necrosis remaining unrecognized. Secondly, our aggressive policy of reoperation for continuing abdominal sepsis meant that the three postoperative colonic complications were detected. In one of these patients, the cause of the colonic perforation was almost certainly iatrogenic, being the result of erosion by a rigid abdominal drain. Thirdly, we developed a fairly low threshold for colonic resection after experience of this complication. This resulted in resection of the colon if its viability was in any doubt, a policy which, as will be discussed

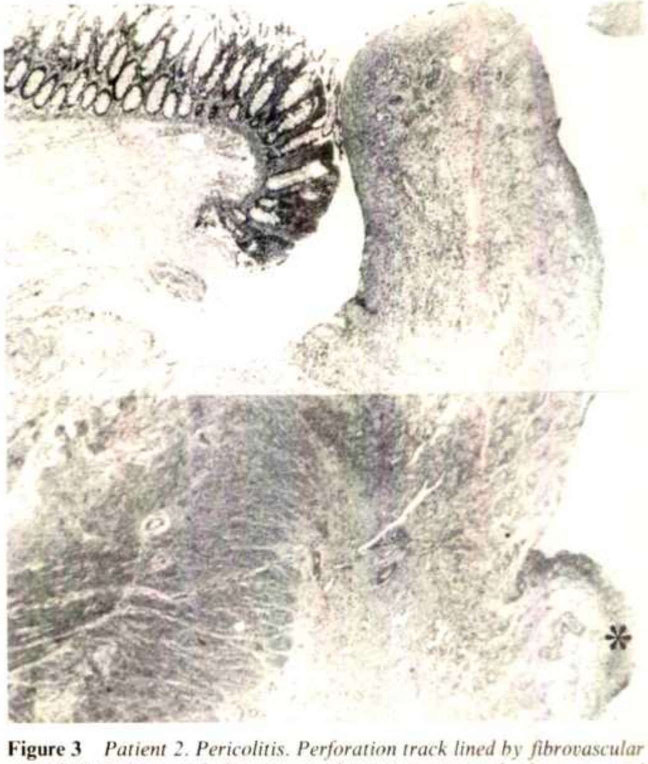

Figure 3 *Patient 2. Pericolitis. Perforation track lined by fibrovascular granulation tissue and showing on abrupt junction with almost normal mucosa. Thick granulation tissue(*) covers the serosal surface. Haematoxylin and eosin, ×35*

Table 3 *A review of the world literature reporting 36 patients with colonic necrosis and/or perforation secondary to severe acute pancreatitis*

Reference	Age and sex		Pancreatic pathology	Colon involved	Outcome
Brette and Maillet (1967)[20]	41	F	Necrosis	Transverse splenic flexure	Died
Colin *et al.* (1968)[21]	53	F	Necrosis	Transverse	Died
Gautier-Benoit *et al.* (1969)[22]	34	M	Abscess	Splenic flexure	Died
Alexandre and Germain (1972)[23]	29	F	Necrosis	Ascending, transverse, descending	Died
Alexandre *et al.* (1974)[24]	45	M	Necrosis	Transverse	Died
	35	M	Necrosis	Transverse	Survived
Champetier *et al.*(1974)[25]	36	M	Necrosis	Transverse	Died
	44	M	Necrosis	Ascending, transverse, splenic flexure	Died
	47	M	Necrosis	Splenic flexure	Survived
Katz *et al.*(1974)[26]	48	F	Abscess	Descending	Survived
Leborgne *et al.* (1975)[27]	39	F	Necrosis	Transverse, splenic flexure, descending	Died
Thompson *et al.* (1977)[7]	—		Abscess	Splenic flexure	—
	56	F	Abscess	Splenic flexure	Died
Dallemand *et al.* (1977)[28]	14	M	Haemorrhagic pancreatitis	Ascending	Survived
	86	M	Necrosis	Descending	Died
Abcarian *et al.* (1979)[29]	33	M	Abscess	Transverse	Died
	35	M	Abscess	Transverse	Survived
Nottle (1980)[30]	58	M	Haemorrhagic pancreatitis	Ascending, transverse, descending, sigmoid	Survived
Flament *et al.* (1981)[31]	50	M	Necrosis	Splenic flexure	Died
	60	M	Necrosis	Splenic flexure, descending, sigmoid	Survived
	63	F	Necrosis	Descending	Died
	63	F	Necrosis	Splenic flexure, descending, sigmoid	Died
	77	M	Necrosis	Total colon	Died
Dubois *et al.* (1982)[32]	68	M	Necrosis	Descending	—
Russell *et al.* (1983)[33]	35	M	Abscess	Transverse	Survived
	49	M	Necrosis, abscess	Transverse	Survived
	50	M	Abscess	Transverse	Died
	63	M	Abscess	Transverse	Survived
	67	M	Necrosis	Descending	Died
Goldofsky *et al.* (1984)[34]	43	M	Necrosis	Descending	Survived
Kukora (1985)[35]	30	M	Abscess	Ascending, transverse, descending	Died
	51	F	Haemorrhagic pancreatitis	Ascending, transverse, descending, sigmoid	Survived
	56	F	Necrosis	Ascending, transverse	Survived
Schein *et al.* (1985)[19]	30	M	Abscess	Transverse, descending	Died
	44	M	Necrosis	Ascending, transverse, descending	Survived
	73	M	Necrosis	Transverse	Died

later, may have resulted in two patients undergoing unnecessary colonic resection. Such a conclusion is easily reached with hindsight. We are not alone, however, in finding a high incidence of this complication in patients with complicated severe acute pancreatitis. Pemberton and co-workers[18] have recently reported 16 patients with enteric fistulae among a group of 81 patients who underwent surgery for pancreatic abscess, making the comment that 'colocutaneous fistulae were particularly common'. Schein *et al.*[19] have reported three patients with pancreatic necrosis or abscess who developed colonic necrosis, all with alcoholic acute pancreatitis and all presenting within a 12-month period.

Analysis of the world series (*Table 3*) shows that: this complication is twice as common in men as it is in women; the median age affected is 48 years with a range from 14 to 86 years; the transverse colon and splenic flexure are by far the commonest sites involved; pancreatic necrosis and pancreatic abscess are equally responsible (see below); the overall mortality rate is 58 per cent. Pancreatic abscess is a somewhat incomplete descriptive phrase which is rarely defined and which is often used synonymously with pancreatic necrosis[36] thus making it likely that necrosis was the underlying pathological process within the gland in most of the cases described. The characteristics of our ten patients were similar to those in the world series: there was a predominance of men (M:F approximately 2:1); the transverse colon and splenic flexure were the commonest sites of involvement; pancreatic necrosis was the commonest underlying cause; the mortality rate was 60 per cent. Our patients, however, were slightly older with a median age of 59 years.

The colonic disorder was variable in the present series and ranged from the changes of 'pericolitis' through to ischaemic necrosis. This spectrum suggests two separate mechanisms of colonic damage. Firstly, direct spread of pancreatic enzymes and peripancreatic inflammatory tissue may involve the serosa of the colon and cause local inflammation and fat necrosis. The proximity of the tail of the pancreas to the splenic flexure has already been discussed in relation to colonic stenosis. Indeed there is sound anatomical support for the hypothesis of direct spread of inflammatory mediators as the reflections of the posterior parietal peritoneum which form the two layers of the transverse mesocolon provide a potential pathway (*Figure 4*). Secondly, thrombosis of mesenteric and submucosal vessels may lead to infarction of the mucosa and deeper layers and the possibility of associated fat infarction and necrosis. Features of both these mechanisms may be seen in some cases and it is possible that the potentially reversible changes of early or mild ischaemia had resolved in some of our patients by the time they came to surgery, leaving only the serosal reaction and fat necrosis.

The exact mechanism of vascular colonic ischaemia in acute pancreatitis is unknown but a number of hypotheses have been suggested. The first is that it may occur as a result of venous infarction by retrograde thrombosis of the superior mesenteric

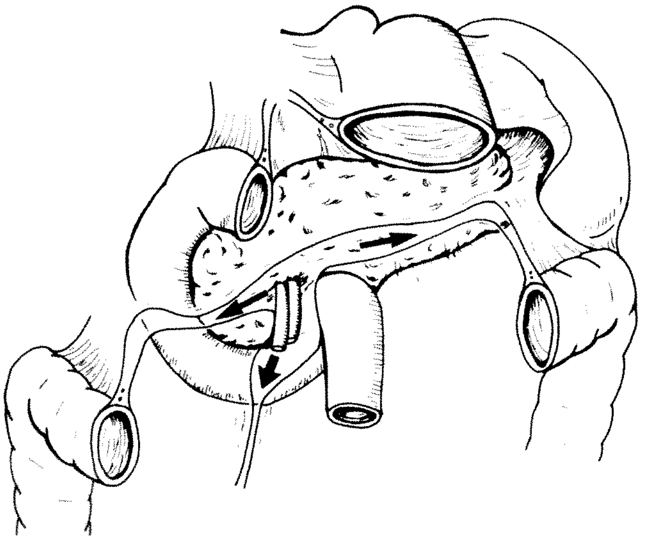

Figure 4 *The peritoneal reflections from the anterior surface of the pancreas provide a route for the spread of pancreatic enzymes and inflammatory products within the transverse mesocolon and the small bowel mesentery*

vein, starting in the splenic vein, as described by Moore and Castleman[17]. The second is that it may arise as a result of thrombosis of mesenteric vessels when oedema and inflammation within the transverse mesocolon result in compression of vessels with consequent slowing of blood flow which, together with systemic hypotension, may predispose to thrombosis. The third hypothesis is that coagulation abnormalities, in particular disseminated intravascular coagulation (which may occur in severe necrotizing pancreatitis[37]), may predispose to mucosal infarction[38]. The last is that sustained hypotension may lead to ischaemic damage and infarction of the colon particularly in an area such as the splenic flexure where the blood supply is often poor (see above). In addition, local pressure on the colon from an adjacent rigid drain may cause necrosis and lead to fistula formation or frank perforation as occurred in one of our patients.

The surgical management of patients with colonic involvement in severe acute pancreatitis remains difficult. The decision whether to resect the colon or not is based on surgical experience and few guidelines can be given. In each of the ten patients in this series, the surgeon considered that a colonic resection was necessary for either non-viability or perforation. On histological examination of the colon, however, only four showed ischaemic necrosis, the remaining six having pericolitis which had perforated in four. In retrospect, therefore, two patients may have undergone unnecessary colectomy. The natural history of pericolitis, however, is unknown in those in whom the colon is left *in situ*. It may be patients in this group who go on to develop a stricture and colonic stenosis if they survive their attack of pancreatitis.

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Appendicitis and appendicectomy in a Melanesian population

H. McA. Foster,
S. J. Webb*

Arawa General Hospital, North Solomons Province, and
**Port Moresby, Papua New Guinea*
Correspondence to:
Mr H. McA. Foster, Hunter Oncology Centre, Newcastle Mater Misericordiae Hospital, Waratah, New South Wales 2298, Australia

A prospective study of patients with appendicitis has been conducted over a 3-year period in the Melanesian population of the North Solomons. Patients presented with suspected appendicitis at an annual rate of 39 per 100 000 population. Appendicitis was confirmed at operation at an annual rate of 22 per 100 000 population. The disease was considerably more frequent in male than in female patients. The annual appendicectomy rate was 29 per 100 000 population. Thirty per cent of patients presented with signs of late or complicated appendicitis, while 37 per cent of patients submitted to operation were found to have advanced appendicitis. The incidence and pattern of appendicitis in the North Solomons are quite different from those seen in the urbanized populations of developed countries.

Keywords: Appendicitis, appendicectomy, laparoscopy, incidence, disease pattern, Melanesia

The incidence and pattern of appendicitis in Melanesians have not been studied in detail or recorded in the literature. Clinical impressions among surgeons working in Papua New Guinea and the Pacific suggest that the condition is not uncommon and may be seen more frequently in semiurbanized Melanesians.

The North Solomons is an island province of Papua New Guinea with a population of around 140 000 Melanesians and 4000 expatriates. The province is served by a single general hospital where virtually all abdominal surgery is performed. This situation provides an ideal opportunity to study the disease in a relatively stable and homogeneous population.

Patients and methods

Records were kept prospectively from January 1983 to December 1985 on all Melanesian patients in the province presenting with suspected appendicitis or undergoing appendicectomy for other indications. Clinical presentation, investigations (including laparoscopy), operative findings and hospital mortality were recorded. Histological examination of specimens was performed by the Department of Anatomical Pathology at Prince Henry's Hospital, Melbourne, Australia.

Results

Over the 3-year period of the study 164 patients presented with clinically suspected appendicitis, giving an average annual incidence of 39 per 100 000 population. Cases proved at operation amounted to 22 per 100 000 population per annum (*Table 1*). Histological evidence of appendicitis was reported at an annual rate of 17 per 100 000 population. Total annual appendicectomy rate was 29 per 100 000 population.

The age distribution of patients presenting with appendicitis is recorded in *Figure 1*. The mean age of female patients at presentation was $22{\cdot}3 \pm 7{\cdot}5$ years and of male patients was $26{\cdot}7 \pm 10{\cdot}3$ years (±s.d.). The difference in mean ages is significant ($P < 0{\cdot}01$, Student's t test).

Late appendicitis was significantly more common in male patients (36 per cent) than in female patients (21 per cent) at presentation ($P < 0{\cdot}05$, χ^2 test, *Table 2*). Thirty-seven per cent of patients (males 42 per cent, females 22 per cent) submitted to operation were found to have complicated appendicitis (*Table 3*).

Appendicectomy was performed at an annual rate of 29 per 100 000 population (males 21 per 100 000 and females 8 per 100 000, *Table 1*). Most patients who underwent appendicectomy did so in the context of appendicitis or its complications. One patient required appendicectomy for technical reasons following exteriorization of an injured colon. The appendix was infrequently removed at operation for other conditions, i.e. '*en passant*'.

Histological examination was obtained in 86 per cent of the 123 appendices removed (*Table 4*). Fifteen specimens were discarded by one surgeon, while all other surgeons and registrars submitted appendices for pathological examination. The operative diagnosis of acute appendicitis was confirmed histologically in 93 per cent of specimens submitted, i.e. 7 per cent of histologically examined appendices considered at operation to be inflamed had no histological evidence of acute appendicitis. In addition, 6 per cent of appendices considered to be normal by the surgeon, and which were submitted to histology, in fact had histological evidence of acute inflammation.

There were no in-patient deaths in this study and all patients were considered to be progressing satisfactorily at discharge. No subsequent deaths have been notified, but detailed follow-up of all patients was not possible after discharge.

Table 1 *Annual incidence of appendicitis and appendicectomy per 100 000 population*

	Males	Females	Total
Clinical diagnosis	24	15	39
Operative diagnosis	17	5	22
Histological diagnosis	13	4	17
Appendicectomy	21	8	29

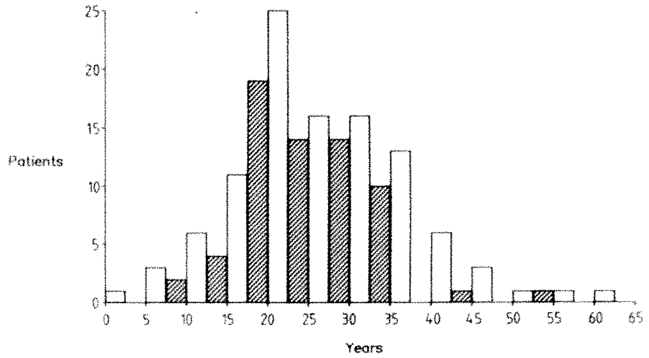

Figure 1 *Age distribution of patients presenting with acute appendicitis over a 3-year period.* □, *Male patients;* ▨, *female patients*

Table 2 *Suspected appendicitis: clinical presentation*

	Males	Females
Abdominal pain	65 (64)	50 (79)
Mass	23 (23)	7 (11)
Spreading peritonitis	13 (13)	6 (10)
Total	101 (100)	63 (100)

Figures in parentheses are percentages

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Table 3 *Operative findings*

	Males	Females
Patients submitted to operation with diagnosis of appendicitis or its sequelae	95	32
Operative diagnosis		
No abnormality	15 (16)	0
Early or equivocal appendicitis	2 (2)	1 (3)
Acute appendicitis	30 (32)	13 (41)
Gangrenous or perforated appendicitis	23 (24)	4 (13)
Appendiceal abscess	12 (13)	2 (6)
Generalized peritonitis	5 (5)	1 (3)
Other abnormality	8 (8)	11 (34)

Figures in parentheses are percentages

Table 4 *Histological audit*

	Males	Females
Appendicectomies	91 (100)	32 (100)
Specimens lost	1 (1)	1 (3)
Specimens discarded	12 (13)	3 (9)
Specimens examined	78 (86)	28 (88)
Histological diagnosis in specimens examined		
Acute appendicitis and sequelae	55 (71)	16 (57)
Normal appendix	20 (26)	4 (14)
Serositis	2 (3)	7 (25)
Carcinoid	0	1 (4)
Carcinoid and abscess	1 (1)	0

Figures in parentheses are percentages

Discussion

The true incidence of appendicitis is difficult to document in any community[1,2]. The true incidence in the North Solomons may have been underestimated in this study as patients in remote areas with mild and self-limiting appendicitis probably do not attend the hospital. In addition, elderly patients with severe appendicitis may not seek surgical treatment and the cause of their death would not be determined as the post-mortem rate is low.

The annual incidence of appendicectomy is easier to ascertain, and in this study the annual rate of 29 per 100 000 population is low when compared with rates from developed countries such as the USA with a rate of about 140 per 100 000 population[3] and Australia with a rate of about 210 per 100 000 population[4].

This difference in appendicectomy rates almost certainly reflects a true difference in the incidence of the disease between the populations. The difference in incidence is perhaps even more striking when it is considered that 62 per cent of the Melanesian population is aged 24 years or less[5] and that appendicitis is a disease of the young[6]. The incidence of proven appendicitis in female patients is about one-third that in male patients (*Table 1*). This difference is significant ($P<0{\cdot}05$, χ^2 test) and is different from developed countries where most studies report only a slight male preponderance[7,8].

Forty-five per cent of patients came from rural areas and were mainly subsistence farmers. The remaining 55 per cent were semi-urbanized, living in small towns and consuming a mixed diet of traditional and 'western' foods. At the 1980 census[5], 85 per cent of the population were recorded as rural, thus appendicitis is much more common in urban Melanesians ($P<0{\cdot}05$, χ^2 test) and may be related to changes in diet or lifestyle[9,10].

The overall incidence of late appendicitis at presentation was high at around 30 per cent. In particular 42 per cent of male patients submitted to operation had advanced appendicitis (gangrene, perforation, abscess or generalized peritonitis) which is higher than the rates of 4–30 per cent published in series from Australia[7], the USA[11] and Denmark[8]. This high incidence seems to be due to delays before patients reach hospital.

Table 5 *Fate of 164 patients presenting with suspected appendicitis*

	Males	Females
Observation only	2 (2)	0
Laparoscopy only	4 (4)	29 (46)
Laparoscopy then appendicectomy	4 (4)	8 (13)
Appendicectomy only	68 (67)	13 (21)
Drain abscess	4 (4)	0
Drain abscess + appendicectomy	9 (9)	0
Laparotomy ± appendicectomy ± drainage	8 (8)	9 (14)
Other operation	2 (2)	4 (6)
Total	101	63

Figures in parentheses are percentages

The clinical diagnosis of acute appendicitis is not easy or reliable, and studies show error rates of up to 30 per cent in male patients and 46 per cent in female patients aged less than 50 years[1,7,11,12]. Language and cultural differences are additional difficulties in the North Solomons. Like other workers[14], we have found laparoscopy to be of value in the diagnosis of appendicitis, especially in young women where 46 per cent of those presenting with suspected appendicitis underwent laparoscopy alone thus avoiding unnecessary appendicectomy (*Table 5*).

This prospective study documents the incidence of acute appendicitis in the Melanesian people of the North Solomons and confirms that the disease is much less common than in the white populations of developed countries. A higher incidence of appendicitis in semi-urbanized and in male Melanesians is also documented.

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High volume lesser sac lavage in acute necrotizing pancreatitis

**O. Teerenhovi,
I. Nordback and J. Eskola***

*Departments of Surgery and Clinical Sciences, Tampere University Central Hospital, Tampere, Finland, and * Department of Clinical Chemistry, Turku University Central Hospital, Finland*

Correspondence to:
Dr O. Teerenhovi, Department of Surgery, Tampere University Central Hospital, 33520 Tampere, Finland

The effect of lesser sac drainage with or without lavage on some early predictors and on outcome in acute necrotizing pancreatitis was analysed. The evaluation was made prospectively for 24 patients, in a single centre study. According to Ranson's criteria and laparotomy findings, the lavage and drainage groups were comparable and the pancreatitis was severe and necrotizing in both groups. In a longitudinal analysis of the first 4 postoperative days, lavage did not show any advantage over drainage, as measured by seven prognostic signs (serum creatinine, blood glucose, base excess, haematocrit, white blood cells, C-reactive protein and immunoreactive phospholipase A_2 concentration). Furthermore, the study did not find that lavage had any positive effect on the incidence of mortality (36 versus 17 per cent in the drainage group) or on septic complications in acute necrotizing pancreatitis. In the total series the extent of pancreatic necrosis was an essential predictor of the outcome.

Keywords: Acute necrotizing pancreatitis, lesser sac lavage, prognostic signs, phospholipase A_2

The two basic problems in severe pancreatitis are early systemic complications due to toxaemia and late septic complications. One treatment method in pancreatitis is peritoneal lavage, which can be carried out non-operatively (by percutaneously placed catheters) or operatively. The treatment of acute necrotizing pancreatitis with peritoneal lavage is based on two supportive measures. It may reduce the amount of toxins present in ascitic fluid[1-3] and wash out peripancreatic debris[4,5]. Previous encouraging results showing early clinical improvement with non-operative lavage therapy[6,7] have not been confirmed in two recent prospective studies[8,9].

The present randomized prospective study in a single hospital was carried out to evaluate the outcome of operative lesser sac drainage with or without lavage in the treatment of acute necrotizing pancreatitis. The effects of this treatment on some selected reliable prognostic factors and on serum phospholipase A_2 concentration were also analysed.

Patients and methods

During the 3-year period from January 1985 to January 1988, 269 patients were admitted to Tampere University Central Hospital with the clinical diagnosis of acute pancreatitis. Our treatment protocol was as follows. The indication for urgent laparotomy was in all cases clinically defined peritonitis. Moreover seven patients had multiple organ failure while in four cases the diagnosis was uncertain. At laparotomy the pancreas was explored by dividing the gastrocolic ligament. In patients with the necrotizing form of acute pancreatitis (26 cases, 9·7 per cent) peripancreatic necrosis was opened by sharp dissection and deep exploration of the pancreas was performed. The necrosis was classified as deep if it extended into the pancreatic parenchyma for a depth of more than 0·5 cm. Two patients were withdrawn from the study because resection of the pancreas was undertaken for total parenchymal necrosis. In all cases with pancreatitis, cholangiography or choledochoscopy was performed and any gallstones were extracted. The biliary tract was intubated via T tube choledochostomy (16 cases) or cholecystostomy (eight cases), without postoperative complications. The peripancreatic drainage was performed with two silicon drains (9 mm inner diameter). One drain was placed from the right to lie close to the pancreatic head and the other from the left to lie behind the splenic flexure of colon close to the pancreatic body and tail. The gastrocolic ligament was not closed.

Thereafter, the 24 patients (8·9 per cent) were randomized to the postoperative lesser sac lavage group or to the drainage group, using the sealed envelope technique. To avoid sequestration of the lavage fluid in the 12 patients with postoperative lavage, a separate catheter (4 mm in diameter) was inserted through a small midline incision below the umbilicus, and was passed into the pelvis. All patients were treated postoperatively in a surgical intensive care unit.

Lesser sac lavage

The lavage fluid was a balanced electrolyte solution without antibiotic addition containing 13·6 mg/ml glucose (Dianeal®, Travenol Laboratories Ltd., Finland). One litre of fluid was infused into the lesser sac for about 15 min and then allowed to drain by gravity for about 45 min. Thus, the daily volume of infused fluid was 24 litres. It was intended to continue lavage for at least 7 days. The mean duration of lavage was, however, 6·9 days (range 4–12; excluding one death on the first day). In five patients the lavage was discontinued before the seventh day. In addition to the one early death, the cause of discontinuation (four patients) was retention of fluid in the abdominal cavity due to the obstruction of the drainage system despite prolongation of the outflow period. Hypertonic dialysate was not used.

Phospholipase A_2

All samples of serum were preserved at −70°C before enzyme assay. Immunoreactive phospholipase A_2 was measured using a time-resolved immunofluorometric assay described earlier[10] with slight modifications. Antiserum to human pancreatic phospholipase A_2 was raised in sheep and purified by immunoadsorption. Solid-phase antibodies were prepared by adsorption of the specific antibodies to the walls of polystyrene microtitration wells (Eflab Comany, Helsinki, Finland). Labelled antibodies were prepared with Eu^{3+}-N′-(*p*-isothiocyanatobenzyl)diethylenetriamine-N^1,N^2,N^3,N^3-tetraacetate[11]. The fluorescence was measured with a time-resolved fluorometer (1230 Arcus®, LKB-Wallac Company, Turku, Finland).

Patients

The patients in the two groups were well matched for clinical and laboratory signs (*Table 1*). Duration of symptoms before operation, operation duration, operative blood loss, volume of ascitic fluid and macroscopic necrosis of the pancreas also correlated well between the two groups (*Table 2*).

Student's *t* test and χ^2 test were used for statistical calculations. The data are expressed as mean ±s.d.

Results

Respiratory insufficiency

The incidences of postoperative artificial ventilation for the lavage and drainage groups were 83 and 67 per cent respectively, the duration of ventilatory support being 11·2 and 14·2 days respectively. During the first 4 postoperative days there was no significant difference in the severity of respiratory insufficiency

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between the lavage group (P_{a,O_2}:F_{i,O_2}, 163) and drainage group (P_{a,O_2}:F_{i,O_2}, 193).

Prognostic factors

Longitudinal analysis of six prognostic signs (serum creatinine, blood glucose, base excess, haematocrit, white blood cell count and C-creative protein) during the first 4 postoperative days did not reveal any significant benefits of lesser sac lavage over drainage alone (*Table 3*). Similarly, longitudinal determination of serum phospholipase A_2 concentration showed no differences between the two groups (*Figure 1*).

Fluid balance

Overall fluid retention in the lavage and drainage groups during the initial 4 days was 360 and 5690 ml respectively ($P<0·01$). The volume of nasogastric aspirate was correspondingly 2370 and 1400 ml. Consequently the need for intravenous albumin (4 per cent) replacement during this period amounted to 3540 and 2050 ml respectively.

Infective complications (Table 4)

Bacterial contamination of ascitic fluid and (possibly as a consequence of this) abscess formation was a more common finding in the lavage group than in the drainage group. The bacteria cultured from ascitic fluid, found on the sixth postoperative day on average, were composed of Gram-negative rods (45 per cent), Gram-positive cocci (45 per cent) and anaerobes (10 per cent). In total, bacterial contamination of ascitic fluid was found in 75 per cent of patients with deep pancreatic necrosis and in 60 per cent of those with superficial pancreatic necrosis.

The indications for reoperation were radiologically verified intra-abdominal abscess (computed tomography in two cases,

Table 1 *Preoperative clinical, laboratory and aetiological data of the patients*

	Lavage group ($n=12$)	Drainage group ($n=12$)
Mean age ±s d	53·3±11·9	55·9±10·0
Sex (M.F)	7:5	8:4
Aetiological factors		
Gallstones	2	4
Alcohol abuse	5	5
ERCP	1	1
Unknown	4	2
C-reactive protein >100 mg/l	9	10
White cell count >16 × 10^9/litre	7	4
Blood glucose >15 mmol/l	3	2
Serum calcium <2·0 mmol/l	11	12
Serum creatinine >230 μmol/l	2	1
The need of artificial ventilation	2	1
Mean Ranson signs ±s d	4·7±1·6	4·5±1·4

ERCP, endoscopic retrograde cholangiopancreatography

Table 2 *Operative data of the patients*

	Lavage group ($n=12$)	Drainage group ($n=12$)
Duration of symptoms to operation (days)	4·1±3·6	2·9±2·0
Duration of operation (h)	2·7±0·9	2·1±0·6
Blood loss at operation (litres)	1·0±0·7	0·7±0·6
Pancreatic necrosis		
Deep	5 (42)	3 (25)
Superficial	7 (58)	9 (75)
Amount of ascitic fluid (litres)	0·6±0·5	0·7±0·4

Data are given as mean ± s.d., except for pancreatic necrosis where the number of patients involved is shown with percentages in parentheses

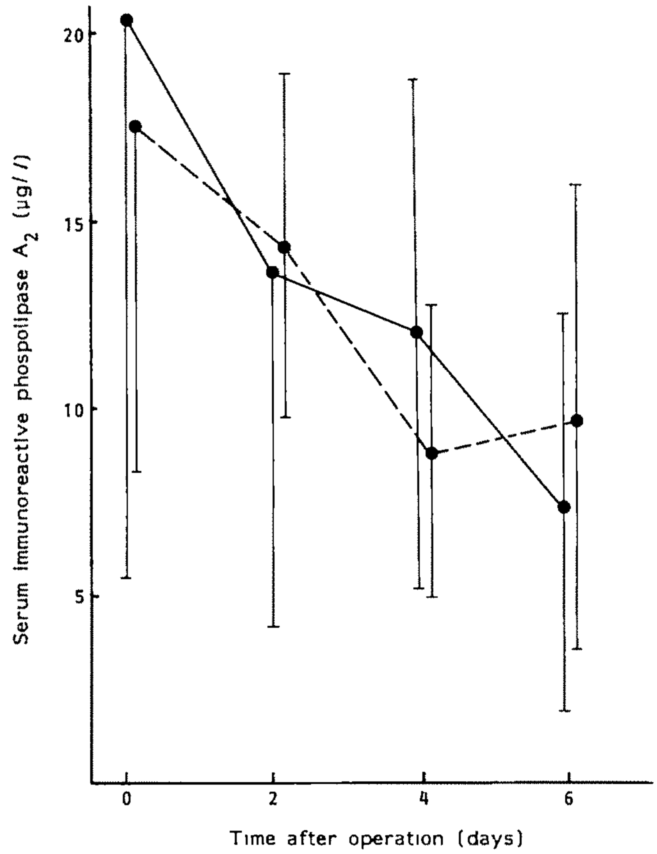

Figure 1 *Longitudinal measurement of immunoreactive phospholipase A_2 concentration in the lavage (——) and drainage (– – –) groups (mean ±s.d.)*

Table 3 *Prognostic signs and C-reactive protein levels preoperatively and during the postoperative period in the lavage and drainage groups*

	Preoperative		Postoperative day							
			1		2		3		4	
	L	D	L	D	L	D	L	D	L	D
Serum creatinine (μmol/l)	140	128	119	106	120	111	125	118	125	98
Blood glucose (mmol/l)	10·4	9·4	12·6	10·7	7·9	10·1	7·5	8·4	7·3	7·1
Base excess (mmol/l)	0·2	−0.8	−0·5	−0·5	3·0	0·3	4·2	1·8	3·3	2·8
Haematocrit	0·41	0·41	0·36	0·38	0·34	0·33	0·31	0·33	0·30	0·33
White blood cell count (× 10^9/litre)	13·6	13·5	16·1	10·8	16·1	12·4	14·5	12·9	17·4	14·5
C-reactive protein (mg/l)	173	192			170	204			178	179

L, lavage group; D, drainage group

Table 4 *Bacterial contamination, development of complications and need for reoperation*

	Lavage group ($n=11$)	Drainage group ($n=12$)
Positive culture of ascitic fluid	9 (82)	6 (50)
Abscess	5 (46)	3 (25)
Sepsis	1 (9)	1 (8)
Pancreatocutaneous fistula	2 (18)	2 (17)
Reoperation	7 (64)*	3 (25)*

Values in parentheses are percentages * $P<0.05$ (lavage group *versus* drainage group)

ultrasound in three cases) or clinically diagnosed intra-abdominal sepsis (five cases). The operative findings were pancreatic abscess (seven cases), other intra-abdominal abscess (one case) and extensive peripancreatic necrosis (three cases). Reoperation for peritonitis or pancreatic abscess was required more commonly in the lavage group. A pancreatocutaneous fistula developed in two patients in each group.

Hospitalization

There was no difference between the lavage and the drainage group in the duration of intensive care (18 *versus* 14 days) or of overall hospital stay (38 *versus* 30 days).

Mortality

When studying the effect of lavage on mortality rate the patient in the lavage group who died of early multiple organ failure on the day of operation was excluded.

Four patients died (36 per cent) in the lavage group and two (17 per cent) in the drainage group. In the total series, the mortality rate in patients with deep pancreatic necrosis was higher (5 of 8, 63 per cent) than in those with superficial necrosis (2 of 16, 13 per cent) ($P<0.01$). *Table 5* shows the mortality rate according to the depth of pancreatic necrosis in both groups According to clinical and autopsy findings the primary causes of death in the lavage group were. multiple organ failure due to septic complications 20 and 21 days after operation (two patients) and haemorrhages into the abdominal cavity 23 and 42 days after operation (two patients) In the drainage group one patient died following myocardial infarction on postoperative day 17 and the other following gastrointestinal haemorrhage on postoperative day 46.

Discussion

The multiorgan failure frequently found in conjunction with severe acute pancreatitis has been thought to be caused by activated pancreatic enzymes escaping into the circulation. Support for this hypothesis has been provided by studies on the ascitic fluid associated with acute pancreatitis. This fluid, which is rich in activated enzymes coupled with antiproteases[12], is very toxic both *in vivo* and *in vitro*[13,14]. Thus peritoneal lavage may be used in treating acute pancreatitis, to wash out toxins and prevent their harmful systemic effects. The results of several experimental[15–17] and clinical studies[6,7,18,19] are in accordance with this hypothesis. Peritoneal lavage has not been shown to reduce peripancreatic septic complications. Of the three previous prospective randomized controlled trials, only the first[7] concluded that peritoneal dialysis was advantageous in treating acute pancreatitis. The later studies showed no effects on mortality, major complications or on hospital stay[8,9].

Two methods of lavage therapy must be distinguished: peripancreatic lesser sac lavage through operatively-placed catheters, and peritoneal dialysis through percutaneously-inserted catheters The theoretical advantage of lesser sac lavage might be the evacuation of the toxins immediately after their secretion into the peripancreatic space before absorption into the circulation. In all three prospective randomized trials mentioned above, peritoneal dialysis was used instead of lesser sac lavage.

The results comparing peritoneal dialysis and lesser sac lavage are contradictory. In a retrospective analysis, Ranson and Spencer[6] found non-operative lavage to be superior to operative lavage, while Büchler *et al*[18] in a partly prospective trial preferred lesser sac lavage, combined in some cases with peritoneal lavage, to peritoneal lavage alone. Lesser sac drainage alone without lavage may also have some favourable influence on the course of acute pancreatitis[20,21] On this basis we designed a prospective randomized study which would investigate only the effect of lesser sac lavage on the course of acute necrotizing pancreatitis. The control patients had operative placement of lesser sac catheters, but did not undergo postoperative lavage

This study has the advantage of being performed in a single centre, but conversely it has the disadvantage of containing only a limited number of patients. In addition to the outcome of the patients we also analysed serum immunoreactive phospholipase A_2 concentrations and some accepted prognostic signs[22,23] for the first 4–6 days

Our results are mainly in accordance with previous prospective randomized studies We were unable to find a significant beneficial effect of lesser sac lavage on prognostic factors or on respiratory insufficiency. Contrary to previous analysis[6,18], we did not find that lesser sac lavage had a favourable influence on early mortality. This disagrees with Stone's prospective randomized trial[7] but agrees with two later studies[8,9]. The depth of the pancreatic necrosis was, however, the dominant prognostic factor in our study (*Table 5*) Moreover, in recent pathophysiological studies, Mayer *et al.*[24] have shown in experimentally induced canine pancreatitis that pancreatic enzymes mainly escape into the circulation via the peripancreatic veins and the lymphatic route, while peritoneal absorption is of minor importance. This is despite the fact that the majority of the enzymes released from the pancreas accumulate in ascitic fluid. Phospholipase A_2 has an essential role in the pathogenesis of acute pancreatitis[25] and its immunoreactive concentration in serum may reflect the severity of acute pancreatitis[26]. In our study, lesser sac lavage had no effect on serum immunoreactive phospholipase A_2 concentration. Normally a patient with severe pancreatitis is well-hydrated with a large third space In our series, lesser sac lavage did not decrease this initial fluid overload. In spite of the use of isotonic dialysate there was, however, less fluid sequestration during the early postoperative course of pancreatitis in the lavage group than in the drainage group. There was obviously a loss of protein in lavage fluid, bearing in mind the large plasma volumes given during the initial days of lavage therapy.

Pancreatic necrosis is often initially sterile[27] Opening the lesser sac can expose the necrotic pancreas to bacterial contamination, and this was also apparent in the present study. Lesser sac lavage did not prevent peripancreatic septic complications. The incidence of ascitic contamination and of abscess formation was particularly high. An explanation might be that the large volume saline wash-outs of the peritoneal cavity can be damaging to peritoneal macrophage function[28]

The present small series suggests that large volume lesser sac lavage does not have a beneficial effect on some early predictors or on the outcome of acute necrotizing pancreatitis.

Table 5 *Mortality rate and depth of pancreatic necrosis*

Mortality	Deep necrosis ($n=7$)	Superficial necrosis ($n=16$)
Lavage group ($n=4$)	3/4 (75)*	1/7 (14)*
Drainage group ($n=2$)	1/3 (33)	1/9 (11)

Values in parentheses are percentages. * $P<0.01$ (deep *versus* superficial necrosis)

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Relationship between bile colonization, high-risk factors and postoperative sepsis in patients undergoing biliary tract operations while receiving a prophylactic antibiotic

**G. R. Wells,
E. W. Taylor*,
G. Lindsay, L. Morton*
and the West of
Scotland Surgical
Infection Study Group†**

*Southern General Hospital,
Glasgow and *Vale of Leven
Hospital, Alexandria,
G83 0UA, UK*

Correspondence to:
Mr E. W. Taylor

A prospective audit of 644 patients undergoing biliary tract operations has been conducted to assess the incidence of bile colonization and its association with the incidence of postoperative sepsis when all patients received the same prophylactic antibiotic. The accuracy of the determination of high-risk factors has been assessed as has the correlation between bile colonization and patients assessed as 'high risk'. Organisms were cultured from the bile of 121 (19 per cent) patients and among these the incidence of wound or intra-abdominal sepsis was 22 per cent whereas among patients with sterile bile the incidence was only 2 per cent ($P<0{\cdot}0001$)*. Although the incidence of bile colonization within the high-risk group (32 per cent) was more than twice that in the low-risk group (14 per cent), more than half (54 per cent) of the patients with positive bile cultures were in the low-risk group. It is concluded that, despite prophylactic antibiotics, bile colonization remains the major factor associated with postoperative sepsis, but that this cannot be predicted accurately by preoperative assessment of high-risk factors. Furthermore, we believe that a policy of selective administration of prophylactic antibiotics solely to high-risk patients cannot be justified.*

Keywords: Bile colonization, risk factors, prophylactic antibiotics, biliary surgery, postoperative sepsis

Patients undergoing biliary tract operations are at a higher risk of developing postoperative sepsis if bacteria are present in their bile at the time of operation[1–3]. Patients who are aged over 70 years, who have obstructive jaundice or common bile duct stones, and those operated on for acute cholecystitis, have an increased incidence of colonized bile[3–5]. The efficacy of antibiotic prophylaxis in these patients is now well established[6,7]. While some authors have concluded that antibiotic prophylaxis can be omitted in patients not fulfilling one of the above criteria[8,9], a recent report has shown that the association between high-risk factors and bile colonization may be less reliable than had been previously assumed[10]. Furthermore, it has been claimed that when prophylactic antibiotics are administered, the organisms responsible for wound infection are exogenous rather than those colonizing the bile[11–13].

An open prospective multicentre audit of patients undergoing biliary tract operations has been conducted to assess the incidence of bile colonization and its association with the incidence of postoperative sepsis when all patients received antibiotic prophylaxis. Ampicillin with sulbactam, a β-lactamase inhibitor, has been used as this combination has been shown to be effective against the organisms commonly isolated from bile cultures[14]. The high-risk factors assessed preoperatively have been compared with the findings at operation. The organisms isolated from the cultures of bile taken at operation have been compared with organisms isolated from postoperative wound infections to determine if the infection was of endogenous or exogenous origin when prophylactic antibiotics were used.

Study design

The value of prophylactic antibiotics in biliary tract surgery is now well established and we considered it unethical to use a placebo or no antibiotic control group to compare the incidence of sepsis. The incidence of infection, when prophylactic antibiotics are used, is generally reported in the range 5–10 per cent and to perform a study to demonstrate a clinically significant difference between two antibiotics in a statistically valid study of acceptable power would have necessitated the enrolment of several thousand patients. Therefore, we considered it more feasible to perform an open evaluation or audit of patients who received the same antibiotic. We sought to enrol 600 patients.

Patients and methods

The study was conducted by 25 consultant general surgeons in ten district general hospitals between May 1986 and October 1987. Patients undergoing operations on the biliary tract were eligible for entry. Patients were excluded if they were under 18 years of age, were pregnant or lactating, or if they had a history of penicillin allergy. Patients were also excluded if they had received antibiotic therapy within 48 h of operation. Ethical committee approval was obtained from each participating hospital and informed consent was obtained from all patients.

The history, clinical examination and preoperative investigations were recorded to assess the risk category. Patients were adjudged to be in the 'high risk' group if they satisfied one or more of the following criteria: age >70 years; the presence of stones or a benign stricture in the common bile duct, perioperative jaundice, carcinoma, emergency surgery (*Table 1*). No additional investigations were performed to improve the accuracy of this assessment.

On induction of anaesthesia all patients received ampicillin 2 g and

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† *A list of participating members of the West of Scotland Surgical Infection Study Group can be found in the Appendix*

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Table 1 *Accuracy of high-risk determination*

Factor	Diagnosed preoperatively	Diagnosed at operation	Incidence of bile colonization
Age over 70 years	109	109	41 (37 6)
Stones in CBD	57	73	23 (32)
Jaundice	52	52	20 (38)
Carcinoma	17	16	5 (31)
Benign stricture	1	4	1 (25)
Emergency operation	6	6	2 (33)
Total (patients)	158 (24 5)	177 (27·5)	56 (31·6)

Values in parentheses are percentages, CBD, common bile duct

Table 2 *Operations performed and incidence of infection*

		Infection		
Operation	Number	Wound	Intra-abdominal	Total number of patients
Cholecystectomy	621	29 (4·7)	12 (1 9)	39 (6 3)
CBD exploration	73	9 (12)	3 (4)	12 (16)
Biliary bypass	23	1 (4)	0	1 (4)
Total (patients)	644	30 (4 7)	12 (1 9)	40 (6 2)

Values in parentheses are percentages, CBD, common bile duct

sulbactam 1 g intravenously. The biliary pathology was reviewed at laparotomy and any change from the preoperative diagnosis was noted Other intra-abdominal pathology, if present, was documented and the operation was performed in the usual manner of the individual surgeon

Bacterial swabs from the external nares were cultured preoperatively and at operation a specimen of bile was taken for culture from the gallbladder or from the common bile duct if this was opened Bile specimens were inoculated into Becton Dickinson Vacutainers® (Becton Dickinson, UK) (Columbia broth with sodium polyethanol sulphonate and increased cysteine, and supplemented peptone broth II) These were incubated for 24 h before being subcultured both aerobically and anaerobically

All patients were reviewed at 6 weeks Infection was defined as the discharge of pus from the wound or as a serous discharge from which bacteria were isolated presenting within 42 days of operation A clinical diagnosis of septicaemia and/or intra-abdominal infection was accepted as a failure of prophylaxis with or without bacteriological confirmation[15]

Statistical analyses were performed using the χ^2 test

Results

In all, 644 patients (164 men and 480 women) were entered with an age range of 19–90 years (mean 53·4). Only six operations were performed as emergencies (within 12 h of admission to hospital), 63 were performed on the next available operating list and 575 were performed as elective procedures.

Cholecystectomy was performed in 621 patients of whom 474 (76·3 per cent) had an operative cholangiogram performed. In 73 (11·7 per cent) exploration of the common bile duct was considered necessary. In 23 patients, either a previous cholecystectomy had been performed or the gallbladder was utilized in a biliary bypass procedure. The overall incidence of sepsis was 6·2 per cent. The incidence of sepsis after different operative procedures is shown in *Table 2*

Preoperatively 158 (24·5 per cent) patients had one or more of the high-risk factors (*Table 1*). At operation 20 patients were found to have stones in the common bile duct not diagnosed preoperatively. Conversely, four patients who had had common bile duct stones diagnosed preoperatively had no evidence of these stones on operative cholangiography. Thus the number of patients who had one or more of the high-risk factors increased to 177 (27·5 per cent) patients.

An organism was isolated from the bile in 121 (18·8 per cent) patients. The organisms isolated were predominantly bowel commensals (*Table 3*). Fifty-six (31·6 per cent) of the 177 patients in the high-risk group had colonized bile compared with 65 (13·9 per cent) of the 467 patients in the low-risk category ($\chi^2 = 26{\cdot}4$, $P < 0{\cdot}0001$).

Patients with colonized bile had an incidence of postoperative infection of 22·3 per cent and there was no significant difference between those in the high- and the low-risk groups (*Table 4*) By comparison, patients who had sterile bile had an overall incidence of sepsis of 2·5 per cent ($\chi^2 = 66{\cdot}3$, $P < 0{\cdot}0001$). In this group the incidence of sepsis in the high-risk category (4·1 per cent) was twice that in the low-risk group (2 0 per cent) but this difference did not reach statistical significance ($\chi^2 = 1{\cdot}76$, $P = 0{\cdot}18$). The correlation between patients with colonized bile and high-risk factors is shown in *Table 4*.

The organisms cultured from wound infections in patients with colonized bile ($n = 27$) were predominantly Gram-negative bacilli and the same organisms were isolated from the bile in 17 (63 per cent) of these patients. In six of the other ten patients, no wound culture was obtained and of the remaining four patients two had a *Staphylococcus aureus* wound infection which was of the same phage-type as the staphylococci isolated from their nares.

However, Gram-positive cocci were cultured from eight (62 per cent) of the 13 bacterial isolates from patients with infection who had sterile bile. Six patients had *S. aureus* wound infections where the same phage-type had been isolated from the nasal swabs and in three patients no wound culture was obtained. Coagulase-negative staphylococci were isolated from the wounds of two patients and an anaerobic coccus from the wound of one patient. In one patient *Clostridium perfringens* and *Escherichia coli* were isolated from both wound and intra-abdominal abscess and the patient subsequently died; this was the only death in the study. This patient underwent a cholecystectomy and the operative cholangiogram demonstrated a narrowing of the distal common bile duct. This was associated with a firm mass in the head of the pancreas and a diagnostic transduodenal Tru-Cut® (Travenol Laboratories Ltd , Illinois, USA) needle biopsy of the pancreas was performed. The biopsy was subsequently reported to be benign. Postoperatively the patient developed necrotizing pancreatitis and died. The bile culture at operation was sterile and *C perfringens* was cultured from the wound and from the pancreatic abscess cavity at repeat laparotomy.

Discussion

The incidence of bile colonization at operation has been reported to range from 16 to 47 per cent[1,9]. In this study we

Table 3 *Organisms isolated from bile*

Organism	Number
Enterobacteriaceae	91*
Staphylococcus aureus	4
Streptococcus faecalis	6
Other Gram-positive aerobes	20
Total isolates	121

* In 49 patients the culture was polymicrobial

Table 4 *Bile colonization and risk*

	Colonized bile		Sterile bile	
Risk	No	Sepsis	No.	Sepsis
High ($n = 177$)	56	12 (21)	121	5 (4 1)
Low ($n = 467$)	65	15 (23)	402	8 (2 0)
Total	121	27 (22·3)	523	13 (2 5)

Values in parentheses are percentages

have found an incidence of 18 8 per cent and the organisms we have isolated are those reported by most authors[8,11,16]. We have not isolated anaerobic organisms but these are not common in the biliary tract[17].

Postoperative infection was significantly more common in patients with positive bile cultures (22·3 per cent) than in those with sterile bile (2·5 per cent, $P<0·0001$) This degree of variation was found in both high- and low-risk groups. A similar result has been observed previously in patients undergoing biliary operations receiving cephalosporin antibiotic prophylaxis[12]. Although we observed a high incidence of infection in those patients with colonized bile our findings compare favourably with the 46 per cent incidence of postoperative septic complications reported by Chetlin and Elliott[3] in patients who had colonized bile and did not receive antibiotic prophylaxis.

Despite the comparatively minor degree of soiling of the peritoneum and wound by bile during surgery, the incidence of infection (22·3 per cent) is similar or greater than that reported after colorectal operations where one might anticipate a much greater degree of bacterial contamination of the operative field. Our results indicate that the soiling of the wound by colonized bile is the cause of sepsis and this raises the interesting problem of how many bacteria are necessary to cause sepsis. In this study, we have not attempted to quantify the number of bacteria in the bile nor the number contaminating the wound and peritoneal cavity. This problem has been assessed in colorectal operations[18] but similar work in biliary tract surgery does not appear to have been done.

The high incidence of postoperative infection in patients with colonized bile despite the use of prophylactic antibiotics is a matter of some concern. In a recent report in which jaundiced patients received tetracycline peritoneal lavage at the time of operation a much lower incidence of sepsis was observed[19]. It is possible that different surgical technique and the use of tetracycline are responsible for this variation. However, our results represent an audit of a number of surgeons rather than one team and we believe they are closer to the experience of most surgeons working in district general hospitals.

An alternative approach might be to attempt to render the bile sterile preoperatively in all patients by antibiotic therapy. However, there must remain doubt as to the efficacy of such a policy which could entail such side-effects as the development of antibiotic resistance or antibiotic-associated colitis.

It has been accepted that infections occurring after biliary tract operations are usually caused by biliary microorganisms[1,8,20]. However, these studies were conducted without antibiotic prophylaxis. When patients are given antibiotic prophylaxis, some authors have contended that postoperative infection may be exogenous in origin[11–13]. In 40 postoperative infections we have found endogenous organisms ($n=17$) to be slightly more common than exogenous ($n=14$). In nine patients with infection no culture was obtained as the infection presented after the patient had been discharged from hospital. Infections occurring in patients with colonized bile were predominantly of endogenous origin, the most common organisms being Gram-negative bacilli, notably *E coli* In contrast, patients with sterile bile who developed wound infections had a higher incidence of *S. aureus*

In this study only those investigations that the participating surgeon considered necessary to confirm the need for biliary tract operation were performed. Our protocol did not require that additional investigations be undertaken to improve the preoperative diagnosis of high-risk factors.

Review of the biliary pathology at operation revealed a preoperative underdiagnosis of common bile duct stones in four false positive and 20 false negative reports. Including these patients, the incidence of colonized bile in high-risk patients was 31 6 per cent, which compares with reported incidences of 39 per cent or greater in patients with similar pathology[3–5].

However, the incidence of bile colonization in low-risk patients in our series was 13·9 per cent which lies within the reported range of 8–19 per cent[4,11]. This confirms the view that a significant proportion of patients without any of the described high-risk factors may have colonized bile[10] and that the incidence of sepsis in this group cannot be neglected. While it could be argued that the incidence of colonized bile in this study is lower than that of previous reports owing to the effect of the antibiotic prophylaxis, previous work has suggested that antibiotics given immediately preoperatively do not sterilize the biliary tract[6,21].

The accurate identification of all patients with colonized bile continues to be difficult. Peroperative Gram staining of the bile has practical difficulties, may be misleading[22] and evidence suggests that antibiotic prophylaxis given after starting the operation is ineffective[23]. We have found a higher incidence of bile colonization in patients with one or more of the high-risk factors (31·6 per cent) than in patients with no risk factor (13·9 per cent). Patients over 70 years of age and those jaundiced at the time of operation were found to have a slightly higher incidence of bile colonization than those undergoing emergency operation or those with stones in the common bile duct.

A recent survey has shown a substantial increase in the number of surgeons using antibiotics prophylactically in biliary tract operations[24]. Whereas most surgeons now accept their use in all patients, there remains a substantial minority of surgeons who administer antibiotics only to patients whom they categorize as being at 'high risk'.

Our study demonstrates that bacterial colonization of bile is associated with a statistically increased risk of postoperative infection The categorization of patients into high- and low-risk groups does not accurately reflect bile colonization and on the basis of our results we believe that a selective policy of antibiotic prophylaxis cannot be justified.

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Appendix

This study was conducted by the following members of the West of Scotland Surgical Infection Study Group:

Mr E. W. Taylor, Mr J. Ross MacCallum and Dr A. Hellyar from Vale of Leven Hospital, Alexandria;
Mr J. Ferguson, Mr G. McBain, Mr H. Tankel and Dr G. Lindsay from Southern General Hospital, Glasgow;
Mr J. Smith, Mr R. Dalling and Dr A. Girdwood from Stobhill Hospital, Glasgow,
Mr M. K. Browne, Mr R. Brooks, Mr R. MacKenzie, Mr I. MacKenzie and Dr J. Thomson from Monklands Hospital, Airdrie;
Mr I. Morrice, Mr G. Bell and Dr V. Biggs from Inverclyde Royal Hospital, Greenock;
Mr K. Mitchell from Royal Alexandria Hospital, Paisley;
Mr D. Bremner, Mr J. Gollock, Mr P. W. Brown and Dr M. Brown from Peel Hospital, Galashiels;
Mr J. McDonald, Mr D. Harper, Mr R. Smith and Dr J. McGavigan from Falkirk Royal Infirmary, Falkirk;
Mr R. Kirby, Mr G. McLatchie and Dr A. Ljunggren from General Hospital, Hartlepool; and
Surg Cdr E. P. Dewar, Surg Cdr R. Leicester and Surg Lt Cdr M. Simmons from Royal Naval Hospital, Haslar, Portsmouth, UK.

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Low power interstitial Nd YAG laser photocoagulation: studies in a transplantable fibrosarcoma

K. Matthewson, H. Barr, C. Tralau and S. G. Bown

National Medical Laser Centre,
University College Hospital,
London, UK
Correspondence to:
Dr K Matthewson, Hexham
General Hospital, Hexham,
Northumberland NE46 1QJ, UK

The effects of interstitial delivery of low power (1·2–2 W), long exposure (600–1200 s) Nd YAG laser light on a transplantable fibrosarcoma in rats have been studied. Three cohorts of ten animals were treated either by 1·2 W for 600 s, 1·2 W for 1200 s or 2 W for 600 s to each tumour nodule. An additional untreated cohort served as controls and a further cohort was treated by radical surgical resection. A partial response as evidenced by ulceration was seen in all laser-treated tumours. In the cohort treated by 2 W for 600 s there was complete loss of palpable tumour, and in five out of the ten animals there was no evidence of local recurrence following a prolonged period of observation. Three of these eventually died from metastatic disease and two were cured. There was a significant prolongation of survival in this cohort compared with the controls (median 70 days versus 30 days, $P < 0{\cdot}05$), but not in any of the other cohorts. Histological assessment of tumours 2 days after laser treatment showed a central area of degeneration with shrunken and densely staining nuclei and disorganized cytoplasm, the boundary between the degenerate zone and surrounding viable tumour being well defined. The technique might be used to induce necrosis of intrahepatic and other solid organ tumours.

Keywords: Nd YAG laser, low power, interstitial, photocoagulation, fibrosarcoma

The use of heat for the destruction of tumours is ancient, the oldest reference being in *The Edwin Smith Surgical Papyrus*, which has been carbon dated to 1700 BC, in which the author describes the treatment of tumours on the breast using the glowing tip of a firedrill[1]. The ancient Greeks and Romans used heat widely as a therapeutic tool and its combination of haemostatic and tissue destroying properties was regarded as particularly valuable[2]. Hyperthermia, or the elevation of whole body or regional temperatures as a primary or adjuvant therapy for cancer, is based on the original observation of Busch in 1866[3] that a histologically proved facial sarcoma completely disappeared after two attacks of erysipelas associated with high fever. Coley in 1893[4] deliberately induced pyrexial states in cancer patients by injecting a toxin consisting of a filtrate from cultured haemolytic *Streptococcus* and *Bacillus prodigiosus*. To reduce the risks of hyperthermia attempts have been made to localize it to the site of the tumour. For deep tissues a variety of non-invasive techniques have been used including radiofrequency current, microwaves and ultrasound. Unfortunately, each has its limitations[5].

Soon after the first description of the ruby laser[6] reports appeared on the use of lasers to treat experimental tumours[7,8]. The ability to transmit laser light along thin, flexible optical fibres has allowed endoscopic delivery of laser light to the gastrointestinal tract and bronchial tree, and the principal use of lasers in the management of cancers has been for recanalization of obstructing lesions at these sites[9–12]. The standard technique is to hold the laser fibre about 1 cm above the tumour and deliver short bursts (0·5–2 s) of high power (50–80 W) Nd YAG laser light into the tumour. Repeated shots vaporize superficial tumour and coagulate deeper tissues. This relatively crude technique can only be used for tumours in hollow organs which are endoscopically accessible, and not for solid organ tumours.

We have recently described a technique for producing necrosis within solid organs using the Nd YAG laser[13]. This involves using very low power settings, of the order of 1–2 W, and long exposure durations (200–1000 s), with the laser fibre inserted into the tissue (interstitial placement). This produces a more gentle heating of tissue which in rat liver produces predictable, well defined necrotic lesions up to 16 mm in diameter. We present here the results of a survival study in rats transplanted with an aggressive fibrosarcoma which was treated using this technique.

Materials and methods

Fifty CBH rats (140–210 g) were transplanted with fibrosarcoma HSN/TC/7. Transplantation was by removing solid tumour (1 g) immediately after the death of the donor animal, and mechanically disaggregating it in a laboratory mixer/emulsifier (Silverson Machines Ltd Chobham, UK) at medium speed in 10 ml normal saline. The solution (0·1 ml) was injected subcutaneously into the flanks of the anaesthetized rats. Further sequential transplantations were undertaken to maintain the tumour line. Tumours grow rapidly to produce a contiguous row of 2–4 tumour nodules 1–1·5 cm in diameter within 21 days.

When the tumour nodules were between 1 and 1·5 cm in diameter, animals were allocated to one of five different treatment cohorts with ten in each cohort. Cohort 1 were controls and did not receive any therapy. Cohorts 2–4 were treated by low power interstitial (LPI) laser therapy. The laser used was a continuous wave Nd YAG laser (Model 212, CVI, Albuquerque, New Mexico, USA) producing invisible infrared light with a wavelength of 1064 nm. The laser light was focused on to the proximal end and transmitted along a 400 μm diameter quartz fibre. A 500 mW helium neon laser aligned coaxially with the Nd YAG laser provided a visible red aiming beam. For treatment the rats were anaesthetized using intramuscular fentanyl citrate and fluanisone (Hypnorm® Janssen Pharmaceuticals Ltd, Oxford, UK). The skin overlying the tumour was penetrated by a 19 G needle through which the laser fibre was passed into the centre of the tumour nodule. Exact positioning of the laser fibre was assisted by ensuring that the aiming beam produced its diffuse glow in the centre of the nodule. Each nodule of tumour within each rat was treated by a separate exposure to laser light. For cohort 2 this was with 1·2 W for 600 s, for cohort 3 with 1·2 W for 1200 s and cohort 4 with 2 W for 600 s. Cohort 5 received radical surgical excision of the tumour, including abdominal wall if necessary.

After treatment each animal was separately caged and received a standard laboratory diet. Each was weighed twice weekly. The dimensions of any residual or recurrent tumour mass and of any ulceration following therapy was also measured twice weekly. The approximate tumour volume was calculated from these measurements

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by assuming that the tumour was cylindrical. Any animal in which the tumour reached 6 cm in length or 3 cm in breadth was killed as tumours of this size caused difficulty with walking. Animals which died without evidence of local recurrence underwent autopsy

Ten additional animals treated by LPI laser photocoagulation were killed 2 days later to assess tumour histology. Evans' blue was injected intravenously before killing. This dye is taken up by viable but not necrotic tumour and facilitates macroscopic determination of the amount of necrosis. Histological sections were prepared using a haematoxylin and eosin stain.

Statistical comparisons were made using the Student's *t* test or the Wilcoxon rank sum test when appropriate.

Results

In the control group the fibrosarcoma grew rapidly and all animals, having fulfilled the criterion for tumour size, were killed 25–35 days (median 30 days) after transplantation. Median tumour volume doubling time calculated from individual tumour volume–time curves in the 10 days before killing was 3·7 days. This rapid rate of tumour growth was paralleled by a median increase in weight of 1·5 g/day during this period, compared with a rate of 0·5 g/day in non-transplanted animals of similar age in our laboratory. No spontaneous ulceration of control tumours occurred.

In cohorts 2–4 all animals had some response to LPI laser therapy as evidenced by superficial sloughing and the development of an ulcer over the tumour 2–5 days after treatment. The mean change in tumour volume in these cohorts in the 3 days after laser therapy is compared with the control group in *Figure 1*. In the three laser-treated cohorts the change in tumour volume was significantly lower than in the controls. *Figure 2* shows changes in the mean weights of animals over the same time period, and these reflected the changes in tumour volume. The proportions of animals in cohorts 1–4 which, following therapy, had decreases in tumour volume, decreases in weight, complete loss of palpable tumour, lack of local recurrence and complete cures are shown in *Table 1*. Complete cures were defined as survival of the animal for 150 days after transplantation without evidence of tumour recurrence. Of the three animals in cohort 4 which died spontaneously without evidence of local recurrence, at autopsy two had pulmonary metastases and one had intra-abdominal metastases. In those animals without local recurrence the ulcer healed with scarring.

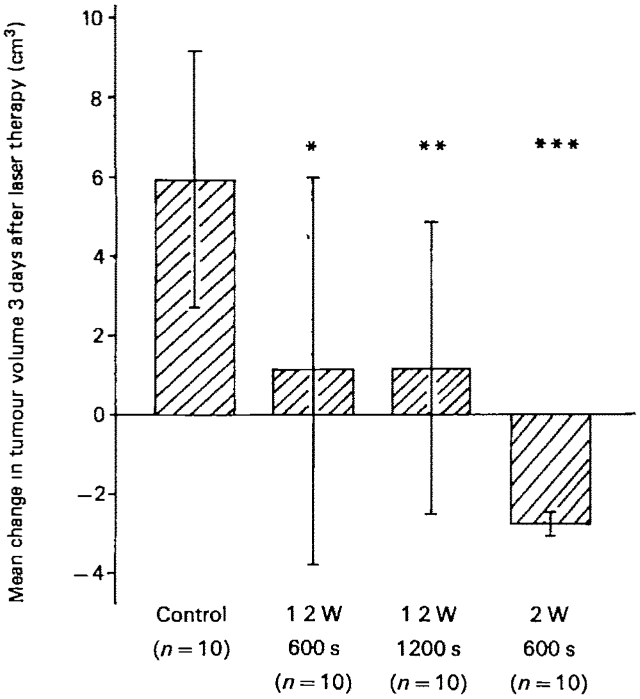

Figure 1 *Mean change (+s d) in tumour volume 3 days after laser therapy Significance values refer to comparisons with the control group* $^{*}P<0{\cdot}02$, $^{**}P<0{\cdot}01$, $^{***}P<0{\cdot}001$

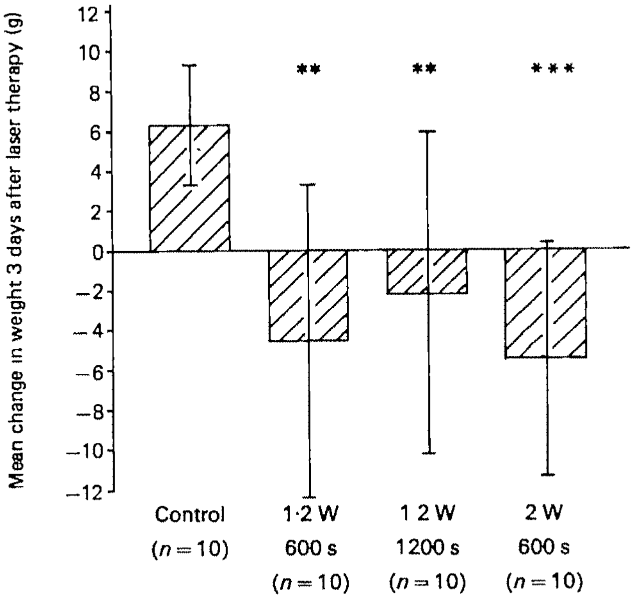

Figure 2 *Mean change (+s.d.) in animal weight 3 days after laser therapy. Significance values refer to comparisons with the control group* $^{**}P<0{\cdot}01$, $^{***}P<0{\cdot}001$

In cohort 5 (the surgical cohort), five animals died within 14 days of surgery, presumably as a consequence of it, as no recurrent tumour was apparent. Four were killed because of a large recurrent tumour 28 days after surgery and one animal was cured. Overall survival from the day of transplantation is shown for all five cohorts in *Figure 3*. Cohort 4 showed significantly prolonged survival compared with the control group but there were no other significant differences in this regard between any of the other groups.

Histological examination of tumours in animals killed 2 days after LPI laser therapy showed a central area of degeneration in which cell nuclei had become shrunken and densely staining and cytoplasm was disorganized. There was a well defined boundary between this degenerate zone and surrounding viable tumour with little evidence of any inflammatory response in the boundary. Histological examination of tumours in animals killed more than 2 days after treatment was not practicable as they simply consisted of a mass of sloughing debris.

Discussion

This study has demonstrated that it is possible to produce necrosis of transplanted fibrosarcomas in rats by prolonged interstitial exposure to low power Nd YAG laser light The best results were obtained in the rats of cohort 4 in which each nodule of tumour was treated with 2 W for 600 s. Using these parameters, all ten animals treated had complete loss of palpable tumour. In five there was no evidence of local recurrence and, although three of these animals died from metastatic disease, two were cured. Animals in this cohort had a significantly prolonged survival compared with those in the control cohort and there was a trend towards a prolonged survival compared with the others. The choices of power and exposure duration were based on a study of the effects of this technique in normal liver[13] which showed that, for a given quantity of energy, the extent of necrosis increased with increasing power with a plateau effect above 1 W and, for a given power setting, increased with increasing total energy with a plateau between 600 and 1000 J Liver and fibrosarcoma have different optical properties and optimal parameters in liver are unlikely to be optimal in fibrosarcoma. It is possible that although 2 W for 600 s produced the best results in this study, other combinations of power and exposure duration could product superior results.

Temperature estimations using microthermocouple arrays close to a laser fibre tip emitting 2 W in liver[13] have shown

Table 1 *The numbers of animals with ulceration over the tumour, decreases in tumour volume, decreases in animal weight, complete loss of palpable tumour, lack of local recurrence and complete cure following low power interstitial Nd YAG laser therapy*

	Cohort 1 Controls ($n = 10$)	Cohort 2 1·2 W, 600 s ($n = 10$)	Cohort 3 1·2 W, 1200 s ($n = 10$)	Cohort 4 2 W, 600 s ($n = 10$)
Ulceration over tumour (n)	0	10	10	10
Decrease in tumour volume (n)	0	5	4	10
Decrease in animal weight (n)	0	6	4	9
Complete loss of palpable tumour (n)	0	3	4	10
Absence of local recurrence (n)	0	0	0	5
Cures (n)	0	0	0	2

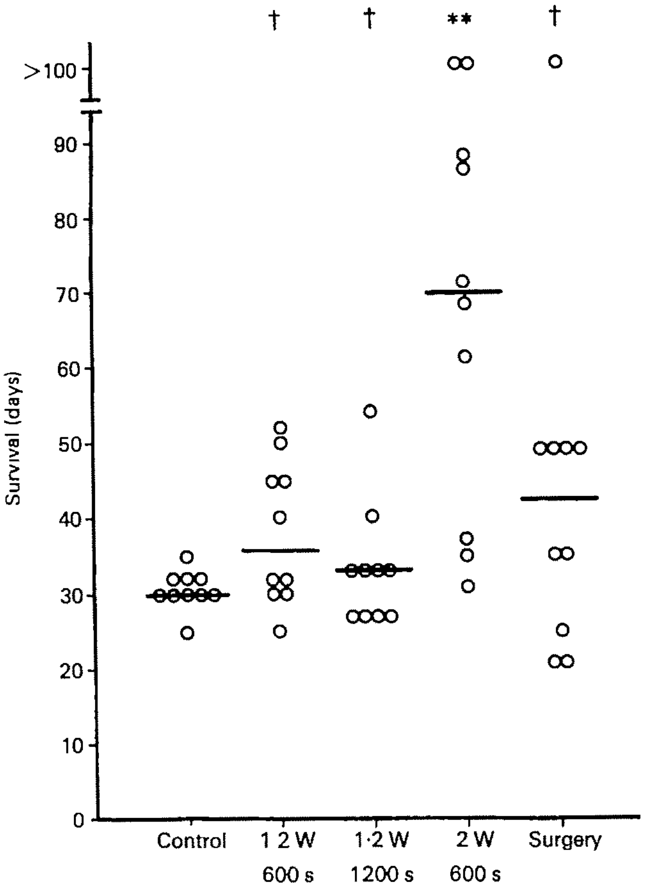

Figure 3 *Duration of survival of treated and untreated CBH rats from time of transplantation with fibrosarcoma. Horizontal bars denote median duration of survival. Significance values refer to comparisons with the control group* ** $P < 0·01$, † *n.s.*

temperatures up to 100 °C at the tip with a fairly rapid fall off to 50 °C 8 mm away. Combinations of temperature and time sufficient to produce necrosis were consistent with a purely thermal effect and not a specific effect of laser light. Histological changes in the fibrosarcoma were analogous to those found in liver in that there was a well defined demarcation between necrosing and viable tissue with the early changes of shrunken, darkly staining nuclei in the affected area and degeneration of the cytoplasm. Whereas liver healed by granulation and fibrous replacement of the necrotic area, the necrotic part of the fibrosarcoma completely sloughed off.

This particular tumour model was chosen because it was a convenient means of rapidly producing a single accessible tumour in rats on which survival studies could be performed. The technique has also been used on chemically induced colorectal adenocarcinomas in rats, a model which more closely approximates a human tumour[14]. Using this model it was possible to treat and destroy all colonoscopically accessible tumours. It was not possible to perform survival studies because with this model tumours develop along the whole length of the bowel. The present study has demonstrated that local tumour can be completely destroyed without recurrence during a prolonged period of observation.

A variety of invasive and non-invasive techniques have been used to produce local hyperthermia of tumours. Radiofrequency current, microwaves and ultrasound are all non-invasive but there are major limitations to their use[5,15]. In the cases of radiofrequency current and microwaves: they are absorbed by water-containing tissues and this may cause problems in tissues containing or surrounded by fluid, their depth of dose is limited to a few centimetres unless multiple applicators are used, the fat near the fat–muscle interface may overheat due to reflections, and they may interfere with metal temperature measuring devices. Ultrasound waves are highly absorbed by bone, causing bone heating and, because they are not transmitted through air cavities, they cannot be used in the lung or abdomen. Invasive techniques which have been described include the implantation of electrodes or thermoseeds which are then exposed to a magnetic induction field[16]. These require surgical placement and a further surgical procedure to remove them unless a foreign body is to be left. Microwaves can also be delivered directly to the tumour site via an applicator inserted into the tissue[17]. The applicator is larger than a typical optical fibre for interstitial laser therapy and the amount of necrosis produced per exposure appears to be less.

A technique which has some similarities to LPI Nd YAG laser therapy is photodynamic therapy (PDT)[18,19]. This involves systemic administration of a photosensitive dye which is taken up with some degree of selectivity by malignant tumours. When the dye is illuminated with light of a particular wavelength, a local cytotoxic effect is produced mainly on the tumour vasculature which causes local tumour necrosis. The light is conveniently produced by a dye laser which can be tuned to produce the appropriate wavelength and it can also be delivered interstitially. The degree of selectivity between tumours and adjacent normal tissue is not great but, with careful adjustment of the treatment parameters, it can be exploited to give some degree of selectivity[20]. There are a number of advantages of LPI Nd YAG laser therapy compared with PDT: no photosensitizer is used and the side-effect of generalized photosensitization is thus avoided; large blood vessels in the treated area are occluded during therapy[13] and bleeding as the tumour sloughs off is not seen as in photodynamic therapy; and infrared light from the Nd YAG laser penetrates tissue more deeply than the visible red light used in PDT[21] so larger volumes of tumour may be treated with a single exposure.

The principal attraction of LPI Nd YAG laser therapy is that laser light can be delivered to the required site via narrow diameter flexible optical fibres without the need for the administration of potentially harmful photosensitizing dyes. Using this technique it may prove possible to treat tumours within solid organs such as liver[22] or pancreas[23] in a relatively atraumatic fashion either percutaneously under ultrasound guidance, or at laparoscopy or laparotomy. Large tumours could be treated by multiple insertions of the laser fibre or by activating multiple fibres simultaneously. The technique is being further studied in larger animal models to assess its likely safety and efficacy in human tumours[24].

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Surgical workshop

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Positioning the Verres needle

S. P. Gupta

Unit III, RNT Medical College and Hospital,
Udaipur-313001, India
Correspondence to· Dr S. P. Gupta

During laparoscopy, pneumoperitoneum is achieved by inserting a Verres needle into the peritoneal cavity, before insertion of the trocar and cannula. It is sometimes difficult to judge whether the tip of the needle is in the peritoneal cavity.

The author has observed that when the needle tip has reached the peritoneal cavity, if the abdominal wall is lifted (preferably with both hands) below the umbilicus and the surgeon's ear kept close to the hub of the Verres needle, a hissing sound can be heard. This may be a distinct clear sound that can be heard from a distance or it may be only feebly audible with the ear close to the needle If such a sound is heard, it has been found to be a reliable sign that the needle tip is in the peritoneal cavity.

If no sound is heard, the needle tip is most probably extraperitoneal, the exceptions being when the needle tip is intraperitoneal but its opening is blocked by omentum, or when the needle has penetrated a viscus or blood vessel.

The author has found this sign helpful in many doubtful cases, especially in the obese patient. It has been used in 2000 cases and has invariably been proved to be reliable.

Wheeless[1] described a needle test using saline applied to the hub of the needle and Tamaskar[2] has described a technique in which 1 per cent xylocaine or distilled water is placed inside the needle and the abdominal wall is pulled up with the help of skin clips. The drop of liquid on the top of the needle is sucked into the peritoneal cavity if the needle tip is free and correctly sited in the peritoneum. However, the author has not found the sign described here previously noted in the literature.

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Reduced human peritoneal plasminogen activating activity: possible mechanism of adhesion formation

J. N. Thompson,
S. Paterson-Brown,
T. Harbourne*,
S. A. Whawell*,
E. Kalodiki and
H. A. F. Dudley

Academic Surgical Unit and
**Irvine Vascular Laboratory,*
St Mary's Hospital Medical
School, London W2 1PG, UK
Correspondence to:
Mr J. N. Thompson,
Royal Postgraduate Medical
School, Hammersmith Hospital,
Ducane Road, London W12 0HS,
UK

A unifying pathophysiological hypothesis states that the plasminogen activating activity (PAA) of the peritoneal mesothelium determines whether the fibrin which forms after peritoneal injury is either lysed or organized into permanent fibrous adhesions. The PAA of human peritoneal biopsies was measured using a fibrin plate lysis technique to assess the changes that occur in inflammation and ischaemia, conditions which both produce fibrous adhesions. Activity was found in all biopsies from normal parietal and visceral (appendix, bowel and omentum) peritoneum with no significant site-to-site variation. Inflamed peritoneum (parietal, appendicular and mesenteric) had significantly less PAA compared with normal peritoneum; visceral ischaemia also resulted in a significant decrease of PAA. These reductions in human peritoneal PAA observed in inflammation and ischaemia support the view that mesothelial PAA plays a key part in the prevention of events leading to the production of fibrous adhesions.

Keywords: Peritoneum, adhesions, plasminogen activators

Intraperitoneal adhesions form in the majority of patients following abdominal surgery[1] and also occur after other causes of peritoneal inflammation[1,2]. They account for 25–33 per cent of all cases of intestinal obstruction in developed countries[3] and are the commonest cause of small bowel obstruction[4]. In addition, intraperitoneal adhesions make subsequent abdominal operation more difficult and potentially hazardous.

An inflammatory exudate forms following peritoneal injury and leads to the deposition of fibrin in the peritoneal cavity[5]. All abdominal surgeons are familiar with the delicate strands of fibrin that are termed fibrinous adhesions. These are either lysed by the plasminogen–plasmin cascade or become organized to form permanent fibrous adhesions[6,7,20]. Studies in animals have shown that normal peritoneum possesses plasminogen activating activity (PAA) and that a reduction in peritoneal PAA occurs after direct injury, grafting or excision[6,8,9]. Such peritoneal insults are also associated with the development of adhesions. Although PAA has been investigated in a number of normal and neoplastic human tissues[10,11], there has been little study of human peritoneal PAA with or without concomitant injury or insult[8].

The aim of this study was to measure the PAA of normal human peritoneum and to assess the effect of inflammation and ischaemia on this activity.

Patients and methods

Patients

Peritoneal biopsies were taken from patients undergoing abdominal surgery. Patient details, operative findings and the sites of biopsy were recorded. Patients gave informed consent to inclusion in this study, which was approved by the local ethical committee.

Biopsy technique

Peritoneal biopsies were taken using a disposable, 6 mm diameter biopsy punch (Stiefel Laboratories (UK) Ltd, Wooburn Green, UK). Excessive tension on the peritoneum at the time of biopsy was avoided. All biopsies were obtained as soon as possible after the peritoneal cavity had been opened. Parietal peritoneal biopsies were taken close to the wound edge. Visceral peritoneal biopsies were taken only from tissue that was to be subsequently excised. After the peritoneum had been incised with the biopsy punch, the disc of peritoneum was carefully dissected off the underlying tissues, wrapped in aluminium foil and frozen in dry ice before transfer to a freezer at −80 °C. Whenever possible, paired biopsies were taken from adjacent areas of peritoneum.

Plasminogen activator extraction and assay

Plasminogen activator was extracted from all biopsies and assayed within 4 weeks. The peritoneal biopsies were thawed rapidly at room temperature and weighed. Each biopsy was washed with 0·5 ml rinsing solution (5 mM sodium dihydrogen phosphate, 0·15 M sodium chloride, pH 7·4) and placed into 1 ml homogenizing solution (2·5 mM sodium dihydrogen phosphate, 0·075 M sodium chloride, 0·25 per cent Triton X100 Sigma Chemical Co. Ltd., UK, pH 7·8) in a small plastic tube on ice. The tissues were then homogenized using an Ultra-Turrax (Janke and Kunzel, FRG) homogenizer for 30 s. The homogenates were centrifuged at 12 000*g* for 20 min at 4°C. Aliquots of 0·25 ml of supernatant were stored at −20°C until PAA assay.

PAA in the peritoneal tissue extracts was assayed using a standard fibrin plate technique[12]. A layer of fibrin was produced in the base of 5 cm diameter plastic Petri dishes (Sterlin Ltd., UK) by pouring in a solution containing 0·9 ml buffer (0·03 M sodium acetate, 0·03 M sodium barbitone, 0·02 M hydrochloric acid; pH 7·4), 3 ml of 1 per cent human fibrinogen (KabiVitrum Ltd., Stockholm, Sweden), 0·3 ml human plasminogen (KabiVitrum Ltd., 2·5 units/ml) and 0·2 ml bovine thrombin (Armour Pharmaceutical Co., USA, 20 units/ml). After the fibrin solution had set, a 6 mm diameter well was cut in the centre of the plate. The peritoneal tissue homogenates were brought to room temperature and 20 μl of each specimen was placed in the central well of a fibrin plate. Standard solutions using human urokinase (Sigma Chemical Co. Ltd.,) reconstituted in sterile water were placed on fibrin plates at the time of each batch of assays.

All plates were then incubated at 37 °C for 24 h and the diameter of the zone of lysis around the central well was measured directly by placing the plates on top of a measuring scale. The maximum and minimum diameters were recorded and the mean value used. A standard plot of diameter of fibrin plate lysis against log urokinase was constructed for each assay and the line of best fit calculated using least squares regression analysis. For paired adjacent peritoneal biopsies the mean PAA level was calculated. Lysis did not occur in any assay with the homogenizing mixture alone. Plate lysis was abolished by prior heating at 80 °C for 20 min, confirming that fibrinolysis was mediated through plasminogen. The results for fibrinolysis were expressed in Ploug units of urokinase per square centimetre of peritoneum (PU/cm^2). The lower limit of sensitivity of the assay was 0·9 PU/cm^2. The coefficient of variation of the PAA-assay was 9 per cent.

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Statistical methods

The Mann–Whitney U test was used for comparisons between groups

Results

PAA was identified within the range of this assay system for 271 of 309 (88 per cent) peritoneal biopsies assayed. The Spearman rank coefficient of correlation for PAA measured in paired biopsies taken from adjacent areas of peritoneum was 0·8 ($P < 0·0001$, $n = 140$ pairs). Similar levels of PAA were found in peritoneal biopsies taken from normal parietal peritoneum (median 4·4 PU/cm^2, range 2·5–11·5, $n = 22$), inguinal hernial sac (median 3·2 PU/cm^2, range <0·9–10·3, $n = 11$), normal omentum (median 4·4 PU/cm^2, range 1·6–13·8, $n = 11$), normal appendix (median 6·9 PU/cm^2, range 1·9–14·3, $n = 7$) and normal bowel (median 5·1 PU/cm^2, range 1·8–6·0, $n = 6$). These PAAs were similar to those obtained in endothelial biopsies taken from the long saphenous vein (median 5·6 PU/cm^2, range 4·6–8·0, $n = 4$). There was no significant correlation between the PAA in biopsies of normal peritoneum taken from different sites in the same patients: parietal and omental ($n = 11$), parietal and visceral ($n = 10$) or omental and visceral ($n = 6$).

The peritoneal PAA was lower in biopsies taken from inflamed parietal peritoneum (*Figure 1*). Inflammation in this group was secondary to appendicitis ($n = 4$), perforated duodenal ulcer ($n = 2$), acute cholecystitis ($n = 2$), strangulated small bowel secondary to adhesion obstruction ($n = 2$) and colonic diverticulitis ($n = 1$). A similar reduction in peritoneal PAA was seen in patients with acute appendicitis, both in the appendix serosa (*Figure 2*) and in biopsies taken from the appendix mesentery (normal mesentery: median 5·4 PU/cm^2, range 2·8–11·9, $n = 5$; inflamed appendix mesentery: median 1·7 PU/cm^2, range <0·9–3·2, $n = 8$, $P < 0·01$).

No difference in PAA was detected between patients with peritoneal inflammation who had positive bacteriological cultures obtained from the abdominal cavity and those who did not.

Five patients had biopsies taken from ischaemic visceral peritoneum (two colon, two appendices epiploicae and one small bowel) and the PAA of these biopsies was lower than normal parietal, intestinal or omental biopsies (*Figure 3*).

Discussion

There are many causes of intra-abdominal adhesions, but the importance of tissue ischaemia has received much attention[3]. While ischaemia is a powerful stimulus to adhesion formation, it does not explain those adhesions observed following other peritoneal insults such as chemical or physical injury and bacterial peritonitis. A unifying pathophysiological mechanism for adhesion formation is provided by the hypothesis that the level of PAA of the peritoneal mesothelium (or other exposed tissue surface) determines the course of inflammation towards fibrinolysis or organization[6,7].

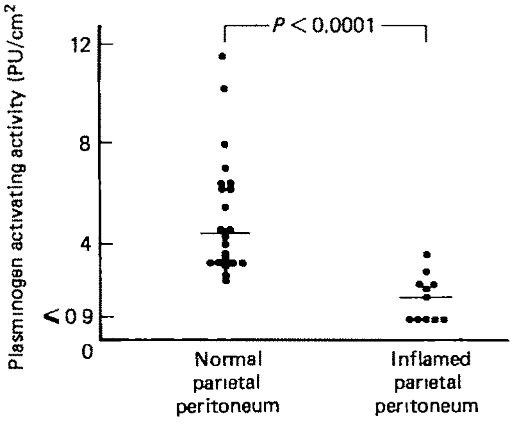

Figure 1 *The plasminogen activating activity of normal and inflamed parietal peritoneum (bars show median values)*

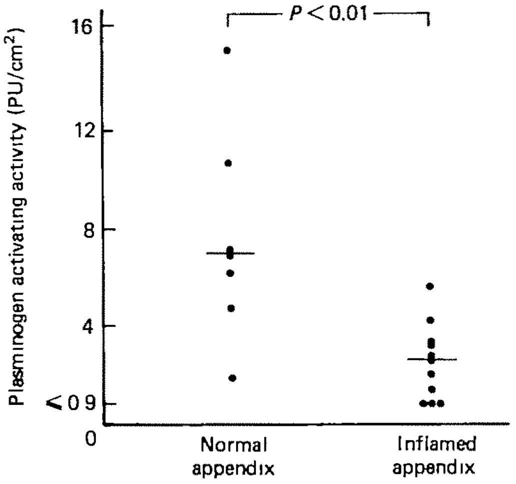

Figure 2 *The plasminogen activating activity of normal and inflamed appendix serosa (bars show median values)*

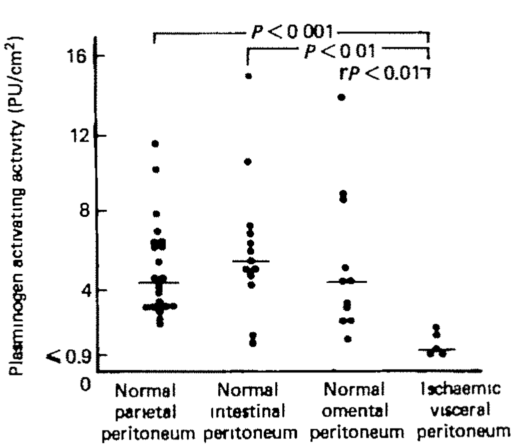

Figure 3 *The plasminogen activating activity of normal parietal, intestinal (including appendix), and omental peritoneum compared with ischaemic visceral peritoneum (bars show median values)*

Plasminogen activator is found in a variety of normal and neoplastic tissues and its main action is to initiate extracellular proteolysis mediated through the plasminogen–plasmin system[13]. Vascular endothelial PAA is important in thrombolysis[14] and, by analogy, it has been considered that peritoneal PAA is important in determining whether fibrinous abdominal adhesions are lysed or organized into permanent fibrous tissue[6–9].

The technique of tissue extraction of plasminogen activator used in this study has been described[15] but not used for the measurement of peritoneal activity. Previous workers have either used the Gelfilm disc (Upjohn, USA) technique[9,16,17,21], or have placed fresh peritoneal biopsies directly on to a fibrin plate[6,8]. The Gelfilm disc technique has the advantage that only mesothelial cells are sampled but it is not possible to be certain that a complete monolayer is obtained or that the remaining peritoneal surface does not contain plasminogen activator. The use of peritoneal biopsies carries the disadvantage that plasminogen activator in submesothelial tissue will also be assayed, although histological studies with the fibrin slide technique suggest that the large majority of plasminogen activator in such biopsies is located in the mesothelium[6–8,18]. We initially tried the Gelfilm disc technique in patients but found very low levels of PAA in discs applied to normal peritoneum.

The present study has demonstrated that normal human peritoneum contains plasminogen activator, that there is little site-to-site variation, and that peritoneal PAA is reduced in inflammation and ischaemia. While previous studies have shown that the normal peritoneal mesothelium of rats, guinea pigs and dogs has PAA[6–9,17,19], and activity has been demonstrated in human small bowel serosa[8] and human mesothelial cell cultures[17]. Only one previous paper reports on a detailed study of human peritoneal PAA. Merlo *et al* showed significant variations in the fibrinolytic activity of normal human peritoneum taken from different sites using the Gelfilm disc technique[21].

The reduction in peritoneal PAA observed after trauma, ischaemia or inflammation seen in this and other studies[6–9] may be related to mesothelial cell injury, mesothelial release of plasminogen activator, or a combination of these mechanisms The time course of such reductions in peritoneal surface PAA may also be important as organization of fibrinous adhesions does not take place experimentally until 5–7 days[6,9]. The timing of these events in man is probably similar, but requires further investigation.

The finding of decreased PAA in patients with peritoneal inflammation and ischaemia, conditions which produce adhesions, supports the unifying hypothesis that a reduction in mesothelial PAA leads to fibrous adhesion formation.

Acknowledgements

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Surgical strategy in primary retroperitoneal tumours

G. Serio, P. Tenchini, F. Nifosi and C. Iacono

Surgical Clinic, Clinica Chirurgica, University of Verona, Verona, Italy
Correspondence to:
Professor G. Serio, Clinica Chirurgica, Università di Verona, 37100 Verona, Italy

Sixty-nine patients with primary retroperitoneal tumours (17 benign, 52 malignant including 4 malignant tumours of uncertain origin) were reviewed to determine the best form of surgical strategy. Total resection was performed in 88 per cent of benign cases and in 65 per cent of malignant cases. In 62 per cent of the total resections for malignant tumours, en bloc *excision included adjacent organs or anatomical structures. Operative mortality rate (in terms of the total number of operations performed) was 5 per cent. Postoperative complications occurred in 14 per cent and recurrences in 35 per cent. The overall 5-year survival rate was 67 per cent in patients with totally resected tumours and zero in patients whose tumours were treated by partial resection or biopsy. An aggressive surgical approach aimed at total excision of the tumour is the best form of therapy currently available. In the totally resected retroperitoneal tumour, the use of adjuvant radiotherapy and/or chemotherapy depends on the grade of the malignancy and clearance as assessed histologically. Careful follow-up based on the use of computerized axial tomography and ultrasound allows early identification of recurrence at a stage when the recurrence is amenable to total resection.*

Keywords: Surgery, primary retroperitoneal tumour

For various reasons surgeons have been unable to agree on any single optimal strategy in the treatment of primary retroperitoneal tumours; 65–86 per cent are malignant[1,2], and, in addition to substantial differences in histology and evolution, they respond differently to adjuvant therapy. Owing to the considerable sizes they may reach, resection of these tumours may be technically difficult, and their relative rarity, with an incidence of 0·07–0·2 per cent of all tumours[2,3], makes it difficult to achieve significant statistical assessment of the different therapeutic tactics available. Moreover, discrepancies in surgical strategy are accentuated in the treatment of recurrences, the incidence of which ranges from 20 to 80 per cent[1,2,4–7].

Patients and methods

Sixty-nine histologically assessed cases were seen in our Institute during the period 1970–78. These comprised primary neoplasms originating in the retroperitoneal cavity excluding lymphomas and primary tumours of retroperitoneal organs (pancreas, kidneys, adrenal glands, urinary excretory tract). There were 35 men and 34 women; the mean age was 48·5 years (range 4–80 years) and the mean duration of symptoms was 6·5 months (range 1–72 months). Palpable masses, with or without pain, were present in 60 cases (87 per cent), gastrointestinal signs in 18 (26 per cent), urinary signs in five (7 per cent), general signs in 18 (26 per cent) and arterial hypertension in three (4 per cent). In two cases the clinical onset of the tumour was acute with a picture of intestinal occlusion and haemoperitoneum. Eleven of the 48 malignant tumours (23 per cent) had already been operated on once or twice elsewhere.

The distribution of the tumours in terms of histological and histogenetic characteristics is summarized in *Table 1*. The maximum tumour diameter of malignant tumours ranged from 13 to 35 cm, benign tumours from 5 to 17 cm. Metastases were observed in 11 of the 47 malignant primary retroperitoneal tumours (23 per cent): 4 out of 31 cases of mesodermal tumour, 6 out of 9 cases of ectodermal tumour, and 1 out of 7 cases of embryonal tumour. The sites affected were the liver (six cases), the skeleton (three cases) and lungs (four cases) and distant lymph nodes (one case).

Up to 1977 the diagnostic techniques available were urography, gastrointestinal contrast radiography and angiography (aortography, selective visceral and parietal arteriography, cavography). Since 1977 all cases have been examined by computerized axial tomography, often in combination with ultrasonography.

Surgical therapy

Fifteen of the 17 benign tumours were treated by total resection and the other two by partial resection and biopsy. Of the 48 malignant tumours and 4 malignant tumours of uncertain origin (paragangliomas), 34 (65 per cent) were subjected to total resection, 14 (27 per cent) to partial resection and 4 (8 per cent) to diagnostic laparotomy. Total resection is defined here as the macroscopic removal of all of the neoplastic mass, regardless of the presence or otherwise of microscopic 'residues' at the resection margins of the tumour or in the tumour cavity.

Local recurrences occurred in 12 (35 per cent) of the 34 malignant primary retroperitoneal tumours subjected to total resection. No recurrences occurred in benign tumours. The total number of reoperations was 18 (six total resections and 12 partial resections or laparotomy, *Table 2*).

Out of 40 total resections (34 first operations and 6 reoperations) for malignant primary retroperitoneal tumours, 25 cases (62 per cent) required *en bloc* excision of adjacent organs or anatomical structures (vessels, skeletal tissue). This also proved necessary in nine (39 per cent) of 23 partial resections. The frequency of the various organs involved in this total of 34 *en bloc* resections is shown in *Table 3*. In the course of 40 total resections for malignant tumour, it was necessary on 17 occasions (42 per cent) to deal with the technical problems relating to involvement of major blood vessels such as the vena cava or aorta or vessels of vital importance (portal triad, superior mesenteric vein). These were solved in various ways: by extended dissection, by *en bloc* resection together with the tumour (vena cava in three cases), or by resection followed by reconstruction (vena cava in one case, superior mesenteric vein in two cases).

Radiotherapy

In our Institute none of the cases was treated preoperatively with radiotherapy. After total resection, adjuvant radiotherapy was given in four cases at doses of 50–70 Gy. Supplementary radiotherapy was given in six cases treated by partial resection, and palliative radiotherapy in three cases of diagnostic laparotomy.

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Table 1 *Histological and histogenetic distribution of 69 primary retroperitoneal tumours*

Primary retroperitoneal tumours	Benign	Malignant	Uncertain malignant	Total
Mesodermal				
Lipoma	2			
Haemangioma	1			
Cystic lymphangioma	1			
Desmoid tumour	1			
Leiomyosarcoma		12		
Liposarcoma		9		
Malignant fibrous histiocytoma		5		
Unclassified sarcoma		3		
Extraskeletal chondrosarcoma		1		
Undifferentiated sarcoma		1		36 (52%)
Ectodermal				
Benign schwannoma	5			
Ganglioneuroma	1			
Neuroblastoma		3		
Malignant paraganglioma		3		
Ganglioneuroblastoma		2		
Malignant schwannoma		1		
Paraganglioma			4	19 (28%)
Embryonal				
Cystic teratoma	2			
Malignant teratoma		2		
Malignant chordoma		2		
Embryonal carcinoma		2		
Seminoma		1		9 (13%)
Debatable origin				
Cyst	4			
Extraskeletal Ewing sarcoma		1		5 (7%)
Total	17 (25%)	48 (70%)	4 (6%)	69

Table 2 *Surgical treatment performed in 69 patients with primary retroperitoneal tumours*

Primary retroperitoneal tumours	Total No	Total resections	Partial resections	Diagnostic laparotomy (biopsy)
Benign	17	15	2	—
Malignant and uncertain malignant				
First operations	52	34	14	4
Reoperations	18	6	9	3
Total	70	40	23	7

Table 3 En bloc *resections in 63 resective procedures (first operations and reoperations) for patients with malignant and uncertain malignant primary retroperitoneal tumours*

Resective procedures	63
En bloc resections	34
During total resections	25/40 (62%)
During partial resections	9/23 (39%)
Organs removed	
Kidney	13
Spleen	7
Pancreas	7
Body–tail	5
Head	2
Adrenal	6
Colon	6
Small intestine	5
Cava	4
Stomach	3
Liver	2
Right lobe	1
Left lobe	1
Rectum	2
Superior mesenteric vein	2
Skeleton	2
Bladder	1
Gallbladder	1

Chemotherapy

Chemotherapy was given preoperatively in only two cases (in one malignant teratoma and in one embryonal carcinoma, both of which had a yolk sac tumour component). After five or six courses of polychemotherapy*, the original tumour masses, measuring 9 and 15 cm respectively, had shrunk to 2.5 and 8 cm maximum diameter, making total resection of the two tumours possible after 5 and 8 months respectively (*Figure 1*). Postoperative chemotherapy was given in three cases after total resection, in five of the cases subjected to partial resection and in three cases after diagnostic laparotomy.

Since 1980 a protocol has been applied to subjects undergoing total resection, which establishes the indication for adjuvant radiotherapy or chemotherapy on the basis of histological typing, tumour grading and the results of a microscopic examination of the suspect areas of the tumour bed (*Table 4*)

Long-term follow-up

In patients undergoing total resection for malignant primary retroperitoneal tumour, the follow-up examination (clinical examination and history, chest X-rays, computerized axial tomography scans and/or ultrasonography, skeletal X-rays or bone scan, monitoring of markers such as urinary vanethylmandelic acid, plasma α-fetoprotein, chorionic β-gonadotrophin, carcinoembryonic antigen) were performed after 3–6 months during the first 2 years and every 6–12 months in subsequent years (*Table 4*)

In patients undergoing partial resection or exploratory laparotomy treated with radiotherapy and/or chemotherapy, follow-up examinations were performed every 3 months in order to evaluate the biological response of the tumour to the treatment and the possibility of further surgery.

Results

Operative mortality

Four patients with malignant primary retroperitoneal tumours (two exploratory laparotomies and two partial resections) died

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* *PVB (cis-platinum, vinblastine, bleomycin), PVA (cis-platinum, etoposide Adriamycin), VLB (vinblastine), CAc (cyclophosphamide, actinomycin D).*

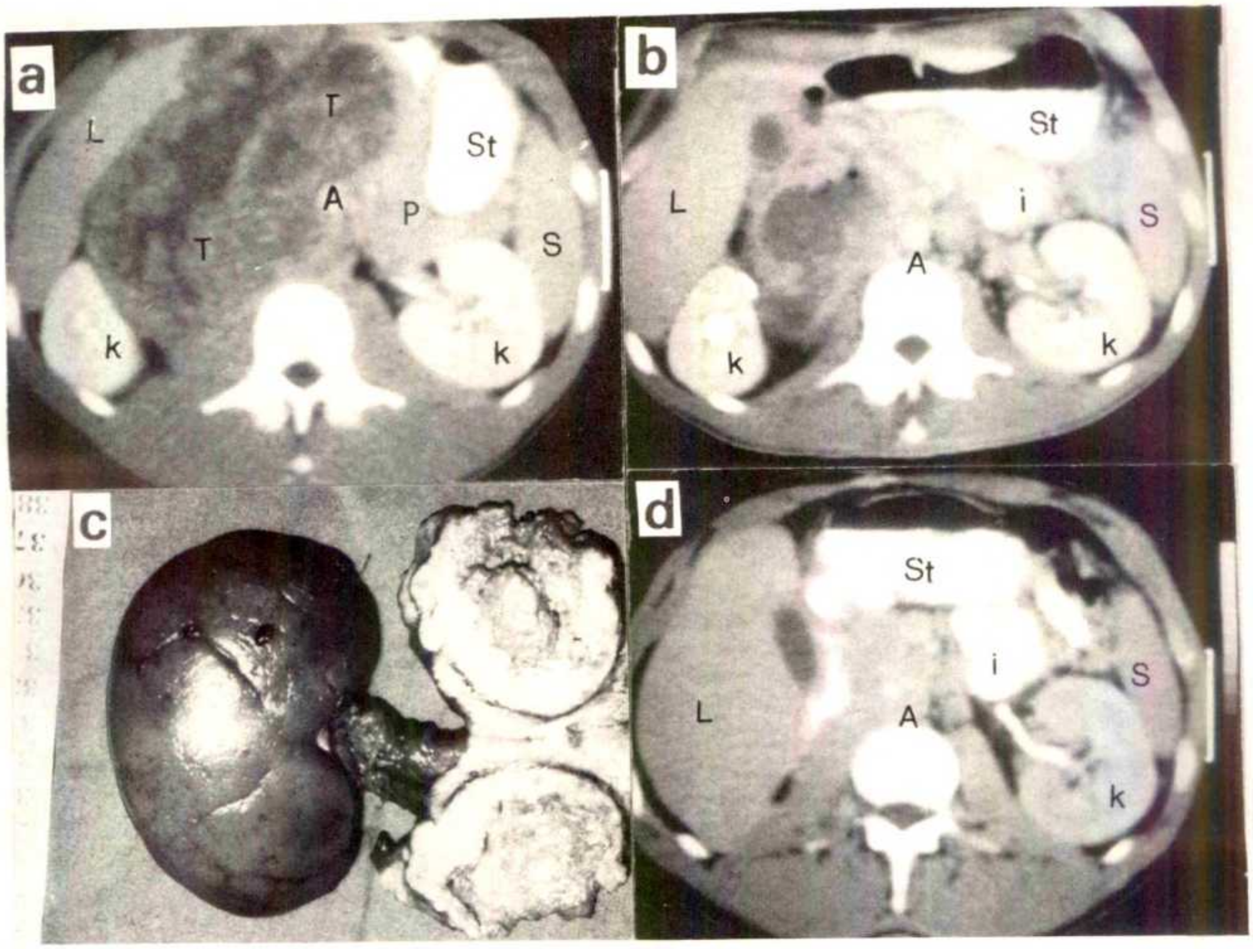


Figure 1 **a** *Computed axial tomography scan of bulky primary retroperitoneal embryonal carcinoma.* **b** *Marked reduction in size after six courses of polychemotherapy.* **c** En bloc *resection of tumour together with right kidney and vena cava.* **d** *No evidence of recurrence at follow-up 2 years after the operation. T, tumour; L, liver; St, stomach; S, spleen; P, pancreas; k, kidney; i, intestine; A, aorta*

Table 4 *Guidelines for adjuvant radiotherapy and chemotherapy and frequency of follow-up for patients with malignant primary retroperitoneal tumours undergoing total resection*

Criteria	Adjuvant therapy	Follow-up*
(A) Low grade PRT rarely metastasizing (well differentiated or myxoid liposarcoma, inflammatory angiomatoid or myxoid malignant fibrous histiocytoma, low grade malignant schwannoma)	None	Every 6 months in the first 2 years; every 2 months in the following years
(B) High grade PRT frequently metastasizing (leiomyosarcoma, lipoblastic and pleomorphic liposarcoma, high grade malignant schwannoma, pleomorphic and giant cell malignant fibrous histiocytoma, rhabdomyosarcoma, neuroblastoma)	CT + RT	Every 3 months in the first 2 years; every 6 months in the following years
(C) In all cases with microscopic residual disease in the tumour cavity	RT	As for A or B, depending on grade

PRT, primary retroperitoneal tumour; CT, chemotherapy; RT, radiotherapy; *computerized axial tomography and/or ultrasonography, chest X-ray, skeletal X-ray or ^{99m}Tc scan, tumoral markers

within 30 days of the operation. In terms of the total of 87 operations or reoperations for benign or malignant tumours the mortality rate was 5 per cent, while in terms of the 70 operations for malignant tumour it was 6 per cent.

Postoperative complications

Complications occurred in 14 per cent of patients and included haemorrhage, peripheral neurological deficits, gastrointestinal fistulae, persistent lymph leaks and cardiopulmonary insufficiency.

Local recurrences

These occurred in 12 (35 per cent) of the 34 malignant tumours subjected to total resection. No recurrences occurred in benign tumours. Recurrences appeared after periods ranging from a minimum of 7 months to a maximum of 54 months (mean 21 months). In patients operated on before 1980 the mean time to appearance of recurrence was 25 months, while in those operated on after this date and included in the follow-up schedule indicated in *Table 4*, the mean disease-free period was 11·5 months. In the four recurrences making up this group the tumours did not exceed 10 cm in diameter (*Figure 2*), were asymptomatic and were all removed by total resection; those observed before 1980 all exceeded 10 cm in diameter (up to 30 cm), were accompanied by clinical signs of compression or by pain and could be completely resected in only two out of six cases.

Metastases

Seven of the 34 patients (20 per cent) undergoing total resection for malignant tumours presented with distant metastases, either accompanied or not by local recurrence. The sites most affected were the liver (four cases), lung and bones (two cases) and peritoneum (one case).

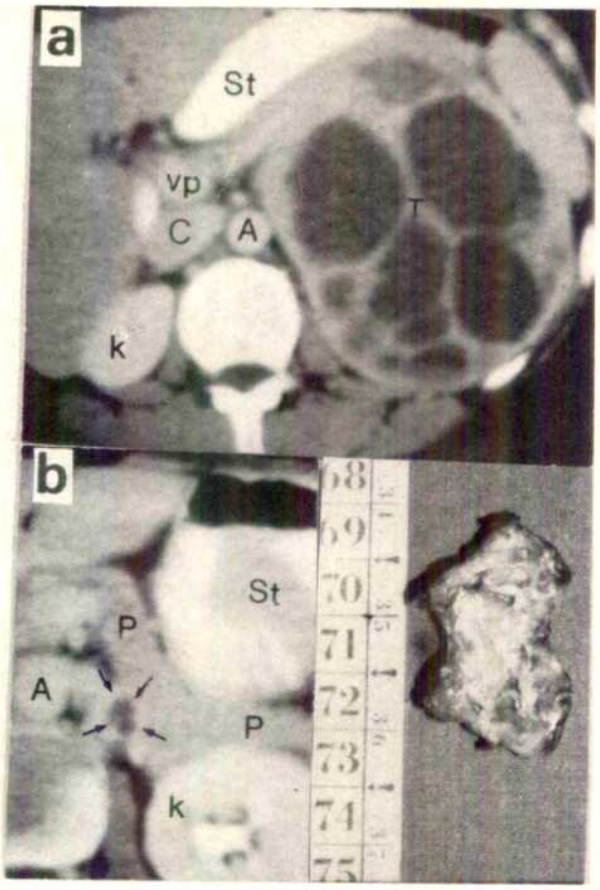


Figure 2 **a** *Computed axial tomography scan of bulky paraganglioma in the left paravertebral gutter.* **b** *Local recurrence of tumour, 2 cm in size (arrows), detected 1 year after the operation. T, tumour; P, pancreas; vp, portal vein; C, cava; A, aorta; St, stomach; k, kidney*

Long-term survival

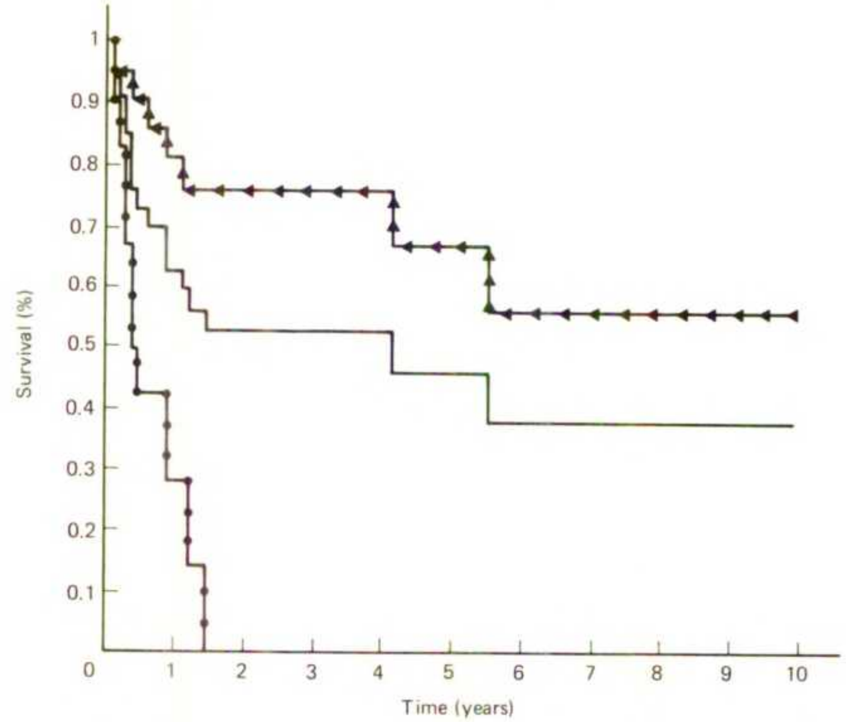
This was evaluated using the product-limit method[8] in 35 malignant primary retroperitoneal tumours. The result was an estimated overall 5-year survival rate of 46 per cent and a 10-year survival rate of 38 per cent with a median value of 50 months (*Figure 3*). There is evidence of a significant difference (log rank 14920, $P < 0{\cdot}0001$) between the survival curves plotted for tumours undergoing total resection (5-year survival 65 per cent, 10-year survival 56 per cent) and those treated by partial resection or simple diagnostic laparotomy (zero survival at 5 and 10 years). Twelve of the 25 sarcomas (40 per cent) were leiomyosarcoma, the poor prognosis of which is borne out by the zero 5-year survival and a median survival of 15 months.

Discussion

The prospects of curing patients with primary retroperitoneal tumours are currently related, as in the past, to the success of total resection of the tumour. Nevertheless, the involvement of important abdominal organs and vessels, which is observed in a very high percentage of cases at the time the neoplasm is diagnosed, is the main obstacle to the implementation of effective surgery.

The incidence of remote metastases ranges considerably, from 5 to 42 per cent of cases[2,4,9], but would appear to be relatively low in recent surgical studies[1]. In the present review, the percentage of metastases was 23 per cent.

A more aggressive surgical approach, expressed in the form of *en bloc* excision of the neoplasms together with adjacent organs or anatomical structures (kidneys, bowel, pancreas, blood vessels), accounts for the significant increase in total resections in recent reviews rather than this being the result of earlier diagnosis. In the present study, total resection of malignant tumours was performed in 65 per cent of cases, which appears to be satisfactory bearing in mind the fact that 23 per cent of the cases had been partially resected elsewhere. This more aggressive surgical approach is not accompanied by an increase in operative mortality rate, which is now con-



◂	17 (81)	13 (76)	7 (67)	5 (56)	5 (56)
—	21 (63)	9 (53)	7 (46)	5 (38)	5 (38)
●	2 (28)	0			

Figure 3 *Overall survival curve for 35 patients with malignant primary retroperitoneal tumour (——). Survival curves for the 23 patients undergoing total resection (◂) and the 12 patients undergoing partial resection or biopsy alone (●). The table shows the number of patients at risk (percentages in parentheses)*

sistently below 10 per cent[1,4,7,10]. It would appear to depend more on the stage of the disease than on the extent of the tissue excision performed[1,7]. In our study the four deaths occurred in subjects with advanced neoplasms; the operative mortality rate in terms of the overall number of operations performed was 5 per cent.

The therapeutic strategy adopted in our Institute for the management of primary retroperitoneal tumour is summarized in the algorithm in *Figure 4*. We should stress that most of the patients suffering from primary retroperitoneal tumour should have surgery, except for a limited number of cases consisting of very debilitated or elderly subjects with metastases, or patients with histologically proved neoplasms whose only prospects of treatment is radiotherapy and/or chemotherapy. In cases where preoperative investigations and surgical exploration provide evidence of a clearly defined mass which can easily be isolated from the adjacent anatomic structures, there is no obstacle to primary total resection of the tumour. In most cases, however, the tumour mass is closely connected (by adhesion or invasion) to one or more organs or important vascular structures and this may require complex *en bloc* excision followed by equally complex reconstruction. In the most recent reviews[1,4,7] this proves necessary in 37–73 per cent of total major excisions, the figure in the present population study being 62 per cent. The risk pertaining to these major resections makes intraoperative histological examination indispensable for the purpose of selecting and excluding from resection those forms in which major excision procedures are not indicated (lymphomas, lymph node metastases, organized haematomas, retroperitoneal fibrosis, giant lymph node hyperplasia) or primary retroperitoneal tumours which are certainly or presumably responsive to radiotherapy and/or chemotherapy (germinal cell tumours, rhabdomyosarcoma, neuroblastoma) which, following suitable treatment, may later prove amenable to surgical treatment (secondary surgery) with a greater chance of success and fewer risks.

The impossibility of performing a total resection should not discourage attempts at partial excision of the tumour, especially in cases where supplementary radiotherapy and/or chemotherapy is planned, as the latter has a better chance of therapeutic success the smaller the tumour mass to be treated[1,4,11].

Recent reviews[1,4,7,10] report overall 5-year survival rates of 30–35 per cent for malignant primary retroperitoneal tumours and retroperitoneal sarcomas. In the latter, survival beyond 5 years does not necessarily depend on eradication of the disease; from a review of cases treated at the Memorial Sloan Kettering Cancer Center in New York, USA[4], it emerges that, while 40 per cent of patients undergoing total resection were still alive at 5 years, only 22 per cent were disease-free.

In the present review, overall 5-year survival of patients with malignant primary retroperitoneal tumours amounted to 46 per cent, while the 10-year survival rate was 38 per cent. The substantial incidence of leiomyosarcomas (28 per cent) adversely affected overall survival.

Recent reviews provide evidence that significant 5-year levels amounting to 40–70 per cent of cases can be achieved only in those subjects whose tumours are amenable to total resection. The results of the present survey confirm this finding: 5-year survival was 67 per cent and 10-year survival 56 per cent in the group of totally resected patients.

Closely bound up with the problem of long-term survival is the question of the treatment of recurrences: in recent reviews the incidence after total resection of the tumour ranges from 50 to 77 per cent[1,4,7]. This high incidence is the same even in groups of patients in whom the resection margins of the neoplasms are tumour-free[7].

It was thought that the postoperative use of chemotherapy and/or radiotherapy might modify this state of affairs. In actual fact, however, no statistically convincing evidence has been found[4,7] for the usefulness of adjuvant radiotherapy and/or chemotherapy, in terms of reductions in recurrence rates and lengthening of the disease-free period, despite the claims of certain investigators[1,12,13].

We believe that an improvement in long-term survival may result from a proper follow-up programme capable of exploiting the diagnostic opportunities afforded by computerized axial tomography and/or ultrasonography and, in certain cases, by a number of specific tumour markers, enabling us to detect small-sized recurrences at the preclinical stage.

As the findings of the present study show, surgery at the preclinical stage offers good prospects of a complete cure. Moreover, the prospects of surgical success achievable in these conditions make it possible to avoid the indiscriminate use of radiotherapy and/or chemotherapy after total resection, such therapy being confined to cases of high grade malignancies or to cases with evidence of persistence of microscopic residues in the tumour cavity.

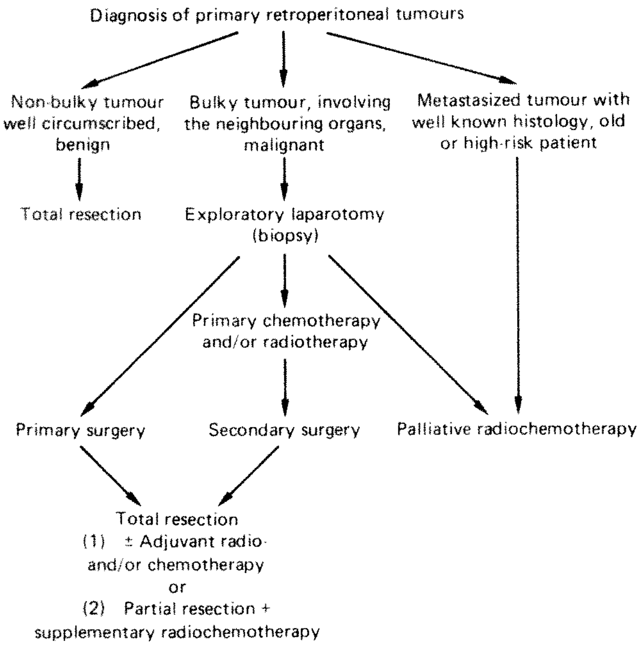

Diagnosis of primary retroperitoneal tumours
Non-bulky tumour well circumscribed, benign
Bulky tumour, involving the neighbouring organs, malignant
Metastasized tumour with well known histology, old or high-risk patient
Total resection
Exploratory laparotomy (biopsy)
Primary chemotherapy and/or radiotherapy
Primary surgery
Secondary surgery
Palliative radiochemotherapy
Total resection
(1) ± Adjuvant radio- and/or chemotherapy
or
(2) Partial resection + supplementary radiochemotherapy

Figure 4 *Algorithm for treatment of primary retroperitoneal tumours*

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Fibroadenoma of the breast: a follow-up of conservative management

S. Wilkinson,
T. J. Anderson, E. Rifkind,
U. Chetty and
A. P. M. Forrest

Department of Surgery (Royal Infirmary of Edinburgh) and Department of Pathology, University of Edinburgh, Edinburgh, UK

Correspondence to:
Professor Sir Patrick Forrest,
Department of Surgery (Royal Infirmary of Edinburgh), University of Edinburgh,
Edinburgh EH3 9YW, UK

This report details the outcome after clinical diagnosis of mammary fibroadenoma in 110 women aged under 35 years. After fine needle aspiration cytology, and subsequent exclusions and failures of follow-up, 92 lesions were observed for a mean of 47 weeks (range 13–90 weeks), with regular measurements until removal of persisting lesions at 12 months. Fifteen lesions disappeared and 56 had the classical histology of fibroadenoma, mean size 2·5 cm; 30 of the latter continued to grow throughout the study. Cytology is essential to exclude malignancy if conservative treatment is considered, and is helpful in identifying a benign lesion. A period longer than 12 months may be required for resolution of a fibroadenoma and removal under local anaesthesia as a day case offers a simple alternative.

Keywords:

In 1985 we reported a retrospective study of 134 patients in whom a clinical diagnosis of fibroadenoma had been made at our breast clinic[1]. On histological examination eight patients had an unsuspected carcinoma (all but one being over 35 years of age) and 58 had a localized fibrocystic change or other benign cause. Thus only 51 per cent had what histologically was considered to be a true fibroadenoma. Similar findings concerning clinicopathological correlations have recently been reported from Cape Town[2]. Realization that the natural history of fibroadenoma was ill-understood stimulated a prospective study to observe the course of fibroadenomas which were clinically diagnosed in women aged less than 35 years, provided fine needle aspiration cytology excluded unsuspected malignancy.

Patients and methods

Between February 1985 and February 1986 all patients attending our breast clinic with a clinical diagnosis of fibroadenoma and who were under the age of 35 years were asked if they would be prepared to enter the study. The clinical diagnosis was agreed by two clinicians, one a consultant surgeon. There was no limit set on the size of the lesion. If consent was given a fine needle aspiration was performed, and fixed and air-dried smears were prepared as previously reported[3]. Provided that the report indicated a smear of satisfactory quality (if not, permission was sought to repeat it) and did not demonstrate any suspicion of malignant cells, arrangements were made to review the patient at a 1 month and then at 3-monthly intervals at a special clinic. At each visit the size of the lesion was measured with engineer's calipers by one of us (S.W.) and at 12 months all persisting lesions were excised. Indications for excision during the course of the study were (1) rapid increase in size of the breast mass, (2) patient requesting removal or (3) patient moving out of the locality. Change in size during the course of the study was determined by comparing the initial size with that measured during and at the end of the study period. This estimate of change was confirmed by independently examining plots of size against time. Lesions were classified as increasing in size, decreasing in size or remaining static. Those regarded as indeterminate were included in the static group.

Results

During the period of study 110 patients had a clinical diagnosis of fibroadenoma. Fourteen were excluded for the reasons given in *Table 1*, and 11 were lost to follow-up. Of the three suspicious aspirates, cancer was confirmed in one patient aged 25, the second lesion was found to be a reactive lymph node on biopsy and the third woman had a normal second biopsy on a poorly defined lesion. Eighty-five patients completed the protocol; the mean time of follow-up was 47 ± 17 weeks (range 13–90 weeks). Seven patients had two fibroadenomas: the total number of clinical fibroadenomas observed therefore was 92.

Natural history

Fifteen of the 92 (16 per cent) clinical 'fibroadenomas' disappeared during the course of the study; 77 persisted and were excised. Twenty-five lesions were excised within 9 months of the start of the study, ten on account of steady increase in size and 15 for reasons given above. The remaining 52 were excised at the end of the study.

Histology

The histology of the 77 persisting lesions was considered to be that of a true classical fibroadenoma (i.e. an encapsulated lesion of typical epithelial and stromal pattern) in 56 cases. Twenty-one were reported as other lesions, mostly fibroadenomatoid nodules (*Table 2*). These are regarded as a type of fibrocystic change which demonstrates focally the epithelial and stromal features of a fibroadenoma[4]. The incidence of a *clinical* diagnosis of fibroadenoma proving to be a classical fibroadenoma on histology was therefore 73 per cent.

Changes in size

Of the 77 persisting lesions 49 increased in size and 28 remained static (including two which possibly became smaller). Increase in size occurred both in those with a proven true fibroadenoma and in the 'other histology' group (*Table 3*).

Table 1 *Reasons for exclusion from study in 110 patients*

Large fibroadenomas in teenagers	2
FNAC	
Acellular aspirates	3
Positive or suspicious of malignancy	3
Pregnancy	1
Refused permission to enter study	5
Total	14

FNAC, fine needle aspiration cytology

Table 2 *Histology of 77 persisting lesions believed clinically to be fibroadenoma*

Fibroadenoma	56
Fibrocystic change	18
Fibroadenomatoid nodule	12
Sclerosing adenosis	1
Sclerosing papillomatosis	1
Fibrotic nodule	3
Group of microcysts	1
Normal breast	3
Total	77

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Table 3 *Growth behaviour of 77 persisting 'clinically diagnosed fibroadenomas' related to their histology*

Histological diagnosis	Increase in size (n)
Fibroadenoma ($n=56$)	40
Fibrocystic change	
Fibroadenomatoid nodule ($n=12$)	6
Others ($n=6$)	3
Normal breast ($n=3$)	0

Table 4 *Age and contraceptive pill usage related to growth pattern of proven fibroadenoma*

Growth pattern	Mean (range) age of patient (years)	Exposed to current OC usage
Increase in size ($n=40$)	23·2 (17–33)	16 (40%)
Static or indeterminate ($n=16$)	24·8 (18–35)	6 (38%)

OC, oral contraceptive

Histological fibroadenomas. Of 56 proven fibroadenomas, 40 increased in size during the study. The mean size reached was 2·5 cm (range 1·0–4·5 cm). Ten reached their maximum size during the first few months of the study and then remained static. The average size attained was 2·0 cm (range 1·0–3·0 cm). Thirty fibroadenomas continued to grow throughout the period of study reaching a maximum mean size of 2·7 cm (range 1·3–4·5 cm) at the time of excision. Fourteen grew to a size exceeding 2·0 cm and four were over 4·0 cm. The relationship between change in size, the age of the patient and contraceptive pill usage is given in *Table 4*. No differences were noted. Pathological size was recorded in all histologically proved fibroadenomas. The relationship between maximum clinical size and pathological size correlated well.

'Other histology' group. Nine of the 21 other lesions increased in size. Six of the 12 fibroadenomatoid nodules increased in size and six remained static. The other three lesions showing an increase in size were reported as fibrotic nodules (two cases) and sclerosing adenosis (one case).

Fine needle aspiration cytology

Fine needle aspiration was reported to be consistent with a fibroadenoma in 60 of 77 patients whose lesions were excised: this judgement was based on a finding of cohesive sheets of clearly benign epithelial cells together with dispersed bare nuclei representing myoepithelial cells[5]. The relationship with the final histological diagnosis is given in *Table 5*. Eight of the 12 fibroadenomatoid nodules had findings identical to those observed for true fibroadenomas. Fine needle aspiration cytology was consistent with a fibroadenoma in six of the 15 lesions which resolved during the period of study.

Discussion

In our previous study we reported that the relationship between the clinical and pathological diagnosis of a fibroadenoma was not exact. The current prospective study confirms this finding and only 56 of 77 lesions (73 per cent) excised on the clinical belief that the patient had a fibroadenoma were pathologically proved to be such. As true fibroadenomas and the pathological conditions mimicking them are now regarded as aberrations of lobular growth and not neoplasms, these difficulties of discrimination on physical examination from other benign alterations of structure may not seem surprising[6,7]. Since many of these 'others' are fibroadenomatoid lesions the discrimination becomes less important. What is important is the discrimination from cancer.

Table 5 *Fine needle aspiration cytology related to final diagnosis in 77 excised breast lumps believed clinically to be fibroadenomas*

Fine needle aspirate	True fibroadenoma	Fibroadenomatoid lesion	Other benign	Normal
Consistent	50	8	2	0
Not consistent	6	4	4	3

In our previous report we noted that eight out of 134 patients with a clinical diagnosis of fibroadenoma had a carcinoma of the breast; these eight patients were all older than 35 years of age. In the present series three patients under the age of 35 years had positive (one case) or suspicious (two cases) reports for malignancy on fine needle aspiration cytology and were therefore excluded from the study. One of these (aged 25 years) was subsequently proved to have breast cancer. Without the availability of fine needle aspiration cytology fibroadenomas, diagnosed clinically, should not be treated conservatively, at least in women over the age of 25 years. Apart from identifying the cases of cancer, fine needle aspiration cytology is useful in that the typical appearances of a 'fibroadenoma' are further evidence of the benign nature of the mass.

The literature on 'fibroadenomas' suggests that they are self-limiting, growing to a size of 2 cm or so and then remaining static. For this reason some manage them conservatively. Our careful follow-up of fibroadenomas over a period of 12 months suggests that not only do most clinically diagnosed fibroadenomas persist but that over half (49 of 92) continue to grow. Some grow for a period and then become static but others continue to show steady growth and may reach over 4 cm in size. However, in contrast to usual teaching, there was no relationship between the age of the patient or oral contraceptive usage and growth pattern.

Growth apart, it is clear from this study that most clinically diagnosed fibroadenomas persist; only a small percentage (16 per cent) spontaneously resolved and less than half of them had fine needle aspirates consistent with a fibroadenoma. Nevertheless, it must be recognized that more than 12 months may be required to bring about satisfactory resolution to the fibrosed stage similar to that occasionally noted by many pathologists as an incidental feature in breast tissue removed for other reasons.

As a result of this prospective study it is reasonable to suggest that a typical clinical fibroadenoma can be treated conservatively in women under 35 years, but only if an adequate cytological smear obtained by fine needle aspiration does not contain malignant or suspicious cells. Careful follow-up is still necessary over a period of 12 months as these lesions may continue to grow. Many may consider it simpler to remove them as a day case under local anaesthesia.

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Surgical significance of non-toxic iodine-avid goitre

M. Kalra and S. K. Khanna

Department of Surgery,
Postgraduate Institute of Medical
Education and Research,
Chandigarh-160012, India
Correspondence to:
Professor S. K. Khanna

During the period 1970–87, of 1580 patients operated on for non-toxic nodular goitre, 17 satisfied the laboratory criteria for iodine avidity. All of these goitres were non-endemic, with no evidence of enzymatic deficiency. Preoperative thyroxine markedly reduced the surgical morbidity by decreasing the size and vascularity of the gland.

Keywords: Goitre, iodine deficiency

Iodine-avid goitre has been discussed in the literature synonymously with endemic goitre, and extensive iodine metabolism studies have been performed in goitrous and non-goitrous subjects of endemic areas[1–3]. Endemic goitres have been classically described as having a high affinity for iodine, with an inverse correlation between the quantity of iodine excreted in the urine and radioactive iodine uptake by the gland[4,5]. However, adjustment to iodine deficiency is surprisingly good provided the deficiency is not too severe.

In endemic goitres no clearly defined biochemical abnormalities have been detected. There is no large reservoir of unused inorganic iodine in these glands and no block in the genesis of hormones. The proteins of the thyroid appear to be normal and antithyroid antibodies are absent[1,4,5].

Non-toxic iodine-avid goitre may not always be endemic in origin. This variety of iodine-hungry glands is sporadically encountered and is not well described in the literature. Clinical recognition of this condition is, however, important to avoid undue morbidity during surgery. Our own experience with this type of goitre over the past 17 years forms the basis of this report.

Patients and methods

Of 1580 patients with non-toxic multinodular goitre operated on in this hospital between 1970 and 1987, 17 patients satisfied the criteria laid down for iodine avidity (*Table 1*). There were five male patients and 12 female patients, with ages ranging from 14 to 65 years. None of the patients belonged to an area in which goitre is endemic, although two gave a history of goitre in the neighbourhood, and one patient had two cousins suffering from goitre.

Clinical examination revealed a massive goitre in eight patients (*Figure 1*) and the others had a moderately enlarged gland. Massive goitre was arbitrarily defined as one extending from the chin to suprasternal notch, and from the outer border of one sternomastoid to the other. In all but two patients, the gland was multinodular. An audible bruit was present in three patients, pressure effects on the trachea and oesophagus were present in three, and one patient had a large retrosternal extension. None showed any clinical evidence of thyrotoxicosis.

The laboratory results for these 17 patients (*Table 2*) showed low or low normal hormone output, a marked tendency to retain iodine, and evidence of markedly increased vascularity on thyroid scan. In the other 1563 patients with non-toxic nodular goitre, the hormone levels and ^{131}I uptake were within the normal range, and the scan showed a patchy uptake. The perchlorate discharge test (performed on five patients) was negative, with ^{131}I discharge 2 h after perchlorate administration ranging from 1 to 5 per cent. Urinary monoiodotyrosine and di-iodotyrosine estimations, to rule out dehalogenase deficiency, were not performed.

Results

Retrospectively, the management could be divided into two phases (*Table 3*).

Phase A (1970–77)

Between 1970 and 1977 iodine-avid goitre was not clinically recognized and both the patients seen in this time period were given Lugol's iodine solution orally for 7–10 days to decrease the vascularity of the gland, as is done in mild thyrotoxicosis. Thereafter, the patients underwent a partial thyroidectomy.

Preoperative iodine led to a marked increase in size of the gland with precipitation of tracheal pressure symptoms in one patient, but the second patient was totally unaffected. At surgery the gland was friable, difficult to handle and extremely vascular, with large surface veins carrying oxygenated blood, an appearance similar to arteriovenous fistula. Surgery lasted for 5–6 h; 6–9 units of blood were transfused and both patients required tracheostomy at the end of the operation. One of the patients had intraoperative hypotension, transient thrombocytopenia (possibly due to massive blood transfusion) and temporary postoperative vocal cord palsy and hypoparathyroidism. Histology of the gland (*Figure 2*) showed evidence of increased vascularity, the follicles containing scanty colloid with hyperplasia of the epithelial lining along with infolding and papillary projections. There was no significant lymphocytic

Table 1 *Criteria for iodine avidity*

Clinically non-toxic goitre
Protein-bound iodine
  Low/low normal
^{131}I uptake
  More than 50 per cent at 4 h
  Further increase in uptake from 4 to 24 h
  Further increase in uptake or plateau from 24 to 48 h
Evidence of increased vascularity on thyroid scan

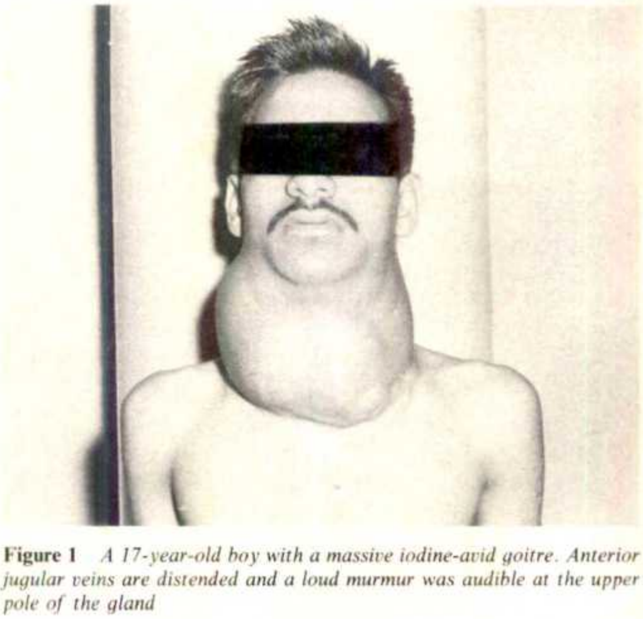

Figure 1 *A 17-year-old boy with a massive iodine-avid goitre. Anterior jugular veins are distended and a loud murmur was audible at the upper pole of the gland*

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Table 2 *Thyroid function tests*

Test	Mean	Range	Normal
Protein-bound iodine (μg/100 ml)	3·8	1·2–5·6	4·0–8·0
^{131}I uptake (%)			
4 h	62·6	50·0–92·0	5·0–15·0
24 h	72·0	53·2–94·0	18·0–40·0
48 h	72·3	54·8–99·0	20·0–40·0
T_3 (ng/ml)	0·9	0·6–1·1	0·8–1·6
T_4 (ng/ml)	63·6	27·0–116·0	40·0–120·0
Thyroid stimulating hormone (units/ml)	4·0	2·6–5·5	0–5·0

Table 3 *Management of iodine-avid goitre: comparative analysis*

	Phase A	Phase B
No. of patients	2	15*
Preoperative therapy	Lugol's iodine solution for 1 week	L-thyroxine for 6 months
Response to preoperative therapy	Unchanged (1/2) Pressure symptoms precipitated (1/1)	Decreased size (12/13) Pressure symptoms relieved (2/2)
Duration of surgery (h)	5·5 and 6	3·2 (mean)
Blood transfused (units)	6 and 9	0–2
Intraoperative hypotension	1/2	0/9
Tracheostomy	2/2	1/9 (tracheomalacia)
Vocal cord palsy	1/2 (temporary)	0/9
Hypoparathyroidism	1/2 (temporary)	0/9
Mortality	0/2	0/9

Phase A, preoperative preparation with iodine; phase B, preoperative preparation with thyroxine; * of the 15 phase B patients, nine had been operated on

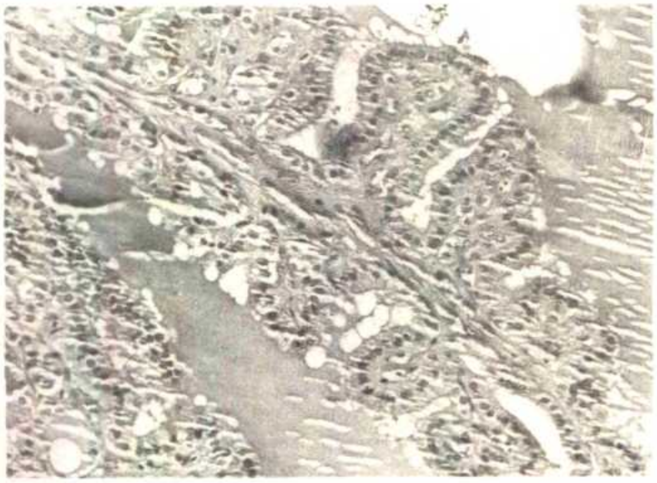

Figure 2 *Photomicrograph of thyroid gland operated on without preoperative thyroxine. The follicles contain scanty colloid with hyperplasia and infolding of epithelial lining (haematoxylin and eosin, magnification × 120).*

infiltration. In the absence of the clinical details, this picture could be easily mistaken for thyrotoxicosis.

Phase B (1978–87)

The clinical entity had been recognized by 1978 and all the patients were given l-thyroxine (0·2–0·3 mg/day) for a minimum period of 6 months before undergoing partial thyroidectomy. There were 15 patients in this group, nine of whom have been operated on so far; four patients are awaiting surgery and two have been lost to follow-up.

Pretreatment with l-thyroxine for 6 months resulted in a marked decrease in the size of the gland (*Figures 3* and *4*) in 12 of 13 patients, with complete relief from pressure symptoms in the remaining two patients. Partial thyroidectomy was technically simple, the gland being firm and easy to excise. Mean duration of surgery was 3·2 h and 0–2 units of blood were required. No significant problems were encountered during or after surgery. Histology (*Figure 5*) revealed a quiescent gland, the follicles being densely packed with colloid and lined by flattened epithelium.

All patients operated on in both groups were given l-thyroxine postoperatively, 0·2 mg daily for 2 years. Follow-up ranged from 2 to 5 years. Goitre reappeared in the pyramidal

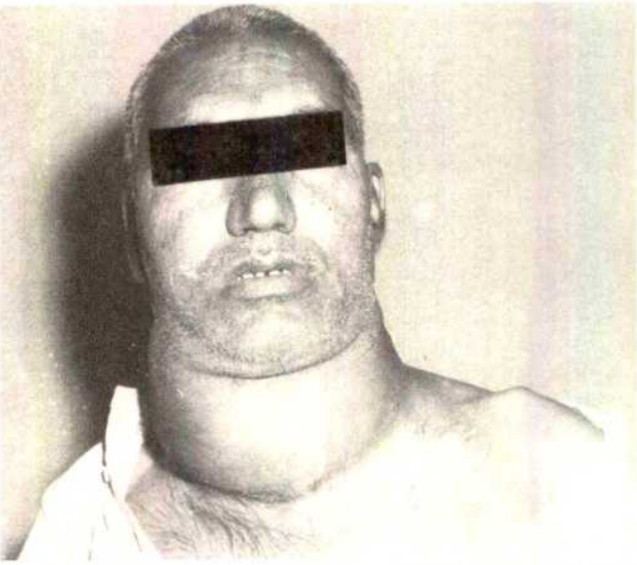

Figure 3 *A 62-year old man with a massive iodine-avid goitre, retrosternal extension and pressure symptoms. Serum T_3 and T_4 levels were in the normal range*

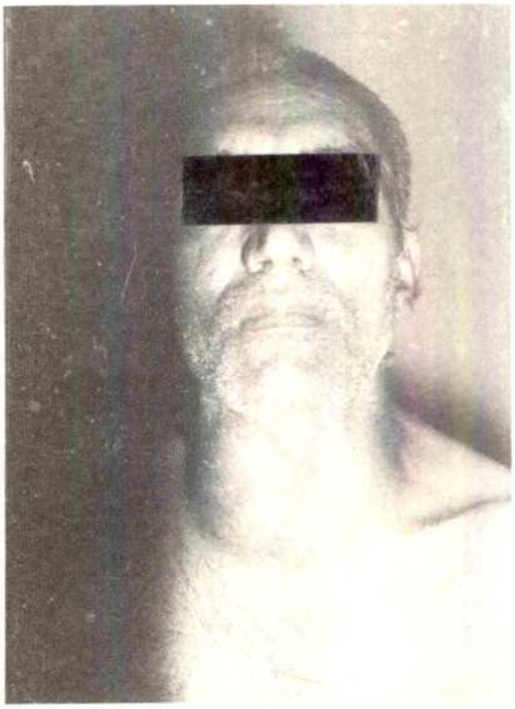

Figure 4 *Same patient as in* Figure 3 *after 6 months of thyroxine. There was a marked reduction in size and complete relief from pressure symptoms*

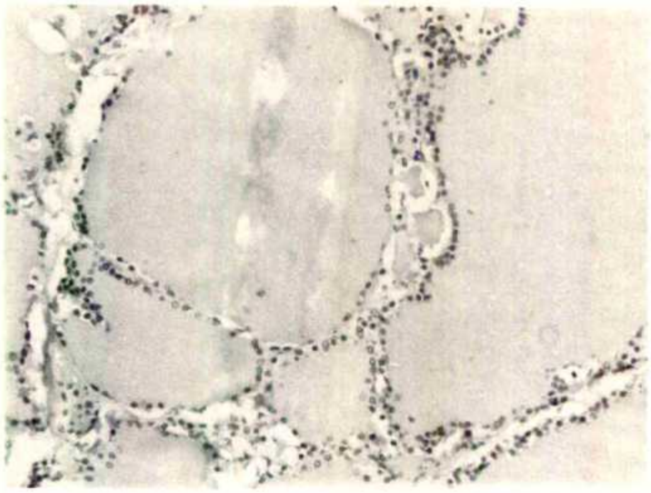

Figure 5 *Photomicrograph of thyroid gland operated on after 6 months of preoperative thyroxine. The gland is quiescent; follicles are densely packed with colloid and lined by a flattened epithelium (haematoxylin and eosin, magnification × 120)*

lobe in one patient, presumably because it was not excised at the initial surgery. In the other patients, including those who have been followed up after cessation of l-thyroxine at the arbitrarily fixed limit of 2 years, no recurrence has been noticed so far. Whether or not a longer period of thyroxine medication is necessary in such patients is not known. Clinically these patients remained euthyroid even after the cessation of thyroxine.

Discussion

There is no single cause of iodine deficiency goitre; it is due to the interplay of many factors, such as the severity of iodine deficiency, the rates of iodine loss from the body, the relative efficiency of the iodine-trapping mechanism of the gland and its biosynthetic activity[1]. However, some authors have tried to suggest that the cause of endemic goitre is faulty iodine utilization owing to impaired organic binding, superimposed on severe iodine deficiency[6]. They have performed perchlorate discharge tests after pretreatment with 2·0 mg potassium iodide and found abnormal discharges in goitrous patients and no discharge in non-goitrous inhabitants of an endemic area. These findings may explain why only part of the population of an endemic area develops goitre, whereas the others adapt successfully to iodine deficiency without the enlargement of their glands. It remains to be proved whether this abnormality is the primary cause of goitre or is a secondary effect. Response of these goitres to iodine administration has also been studied[7], but reported experience of any problems during surgical management is lacking.

However, none of the patients seen in this group with the classical biochemical characteristics of iodine hunger came from an iodine deficiency goitre zone. Therefore, sporadically occurring iodine-avid goitre should be considered a distinct but rare entity. Its aetiology is not clear. It is not congenital because it occurred over a wide age range and the perchlorate discharge test was negative. Dehalogenase deficiency could not be tested for, owing to the lack of laboratory facilities but its involvement cannot be ruled out. Clinically, iodine-avid goitre does not have any distinct parameters to differentiate it from other non-toxic nodular goitres. In this study 47 per cent were massive, 88 per cent were nodular and 18 per cent had a bruit and/or pressure effects. Therefore the diagnosis is based purely on the laboratory criteria laid down.

When surgery was performed without preoperative L-thyroxine the gland was found to be extremely vascular and friable, and bled profusely at the slightest touch. The surgery was therefore prolonged and a large volume of intraoperative blood replacement was necessary. Preoperative thyroxine for an arbitrarily decided period of 6 months decreased the size and vascularity of these goitres, relieved pressure symptoms and greatly diminished the surgical morbidity. The surgical significance of this condition is that it should be recognized before operation and appropriate preparation with thyroxine undertaken if major operative difficulty is to be avoided.

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Splenectomy for massive splenomegaly

J. H. F. Shaw and M. Clark

University Department of Surgery, Auckland Hospital, Auckland, New Zealand

Correspondence to:
Mr J. H. F. Shaw

Twenty-four patients who underwent resection of giant spleen (spleen weight >1·5 kg) have been reviewed to determine the difficulties and benefits of the procedure and, in particular, whether the use of adrenaline injection into the splenic artery could safely reduce technical difficulty. Although morbidity was higher in patients with giant spleens compared with those undergoing resection of smaller spleens the incidence of serious complications was small, and there were no operative or in-hospital deaths. In addition, virtually all patients benefited either on the basis of minimized haematological defect, or palliation of symptoms. Further, the injection of 1 ml of 1:10 000 adrenaline into the splenic artery before splenic mobilization reduced the splenic volume by approximately 40 per cent on average, and resulted in improved exposure, thereby facilitating the procedure.

Keywords: Elective splenectomy, haematological disorders, Hodgkin's lymphoma, overwhelming infections, thrombocytopenia, giant spleen, adrenaline

Elective splenectomy is a frequently used technique in the diagnosis and therapy of a variety of haematological disorders, including the treatment and staging of some patients with lymphoma[1,2], the treatment of hairy cell leukaemia[3] and for diagnosis of inexplicable splenomegaly[4]. However, most reports on the usefulness of splenectomy in the diagnosis and management of haematology patients focus on patients with normal sized, or moderately enlarged spleens, and there has been a widely held belief that resection of giant spleen is associated with major hazards, and that it is ineffective in providing palliation of symptoms and/or correction of haematological[6] abnormalities.

Goldstone[6] reported that splenectomy for massive spleen provided symptomatic relief in some patients, but that this gain was balanced by a high operative mortality rate. In contrast, Wobbes *et al.*[7] and Bickerstaff and Morris[8] have reported that resection of giant spleen can be accomplished with minimal risk of mortality, and that satisfactory palliation and/or correction of haematological abnormalities can be achieved.

Over recent years, most elective splenic surgery in Auckland has been performed by one of two surgeons in one centre. We have reviewed the local experience of splenectomy for massive splenomegaly and, in particular, we have asked: can resection of giant spleen be undertaken safely; is the procedure effective in providing palliation and/or minimizing the haematological defects; is injection of adrenaline into the splenic artery before mobilization of the spleen useful for both patient and surgeon?

Patients and methods

From a total of 148 patients who underwent elective splenectomy at Auckland Hospital (1978–88), 24 had giant spleens (weight >1·5 kg). There were 14 men and 10 women (mean age 60 years). The indications for splenectomy are summarized in *Table 1*.

Seventeen operations were done through abdominal incisions and in seven a thoracoabdominal incision was used. Seven severely thrombocytopenic patients (bleeding times >15 min) received platelet transfusions intraoperatively, and five also required whole blood.

Most commonly the splenic vessels were controlled via the lesser sac before mobilization of the spleen. In the seven patients most recently operated on, 1 ml of 1:10000 adrenaline was injected into the splenic artery after the vessel had been controlled. After the injection, the artery was immediately ligated to maximize the effect of the adrenaline on the spleen while minimizing the systemic effect. The intention was to reduce the volume of the spleen and improve access and ease of dissection, while having only a minor haemodynamic effect (due to the leak of adrenaline into the systemic circulation as part of the contraction of the spleen). After splenic artery ligation the lienorenal ligament was incised, adhesions between spleen and adjacent structures were ligated and divided, and the spleen was mobilized. Finally, the splenic artery and vein were separately ligated.

Pneumococcal vaccine was used routinely (most commonly preoperatively) to minimize the risk of overwhelming postsplenectomy infection. In addition, in order to reduce the risk of wound infection, pneumonia and/or intra-abdominal abscess formation, a single dose of broad spectrum antibiotic was administered on induction of anaesthesia.

Results

The weight distribution of the resected spleens was 1539–3600 g (mean 2142 g), and the final diagnoses are shown in *Table 2*.

Table 1 *Indications for splenectomy in patients with massive splenomegaly*

Indication (primary)	No.
Correction of cytopenia	9
Diagnosis	6
Relief of abdominal pain	4
Rupture	1
Initial treatment (hairy cell leukaemia)	4
Total	24

Table 2 *Diagnoses in patients with massive splenomegaly*

Diagnosis	No.
Myelofibrosis	10
Non-Hodgkin's lymphoma	
Poorly differentiated	2
Large cell	1
Mixed histiocytic and lymphocytic	1
Chronic myeloid leukaemia	1
Chronic lymphatic leukaemia	2
Hairy cell leukaemia	4
Congestive splenomegaly	2
Wilson's disease	1
Total	24

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Table 3 *Effect of adrenaline injection on giant splenomegaly*

	Spleen volume		Blood pressure (mmHg)		Heart rate	
Diagnosis	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
Myelofibrosis	3·3	2·1	140	170	70	90
Hairy cell leukaemia	1·5	1·0	130	135	75	80
Myelofibrosis	2·2	1·3	125	145	65	65
Ruptured chronic myeloid leukaemia	2·6	1·3	150	160	60	68
Non-Hodgkin's lymphoma	3·2	1·8	105	105	65	65
Wilson's disease	1·6	0·9	145	200	70	110
Chronic lymphatic leukaemia	1·8	1·2	135	175	75	75
Mean	2·3	1·4	133	156	69	79

Table 4 *Complications of splenectomy for massive splenomegaly*

Complication	No.
Chest infection	5
Wound infection	3
Pleural effusion	2
Hepatitis B infection	1
Haemorrhage	1
Pulmonary embolus	1
Total	13

The nine patients with cytopenia as the primary indication for splenectomy all had reversal of this problem. Six are alive at an average of 5 months after surgery. Two died at 23 and 36 months after surgery, and the remaining patient was lost to follow-up.

Six splenectomies were performed for diagnosis and a diagnosis was obtained in all. Two had congestive splenomegaly (both alive at 36 months) and the remaining patients proved to have either non-Hodgkin's lymphoma, or myelofibrosis.

The four patients who had palliative splenectomy gained symptomatic relief. One is alive 1 month postoperatively, two died of their malignancy on average 4 years after surgery and another succumbed to overwhelming postsplenectomy infection (pneumococcal meningitis) after 5 months. Five other patients who underwent splenectomy primarily for reasons other than relief of pain also experienced relief from intra-abdominal mass symptoms.

The splenectomies undertaken as initial treatment of hairy cell leukaemia were all successful, either as sole treatment of the leukaemia, or as an adjunct to interferon, and all were alive at the time of the study. The patient who had resection of ruptured giant spleen (secondary to chronic myeloid leukaemia) is alive and well at 1 year, and the patient who underwent splenectomy (and splenorenal shunt) for Wilson's disease is also alive after 1 year.

The alterations in splenic volume, blood pressure and pulse rate following the injection of adrenaline are summarized in *Table 3*.

There were no in-hospital deaths and complications are summarized in *Table 4*.

Discussion

The major goals of our study were to assess whether resection of giant spleen is a safe procedure with an acceptable complication rate, to determine whether the procedure was an effective means of palliating symptoms and/or reversing haematological abnormalities, and to assess whether the intra-arterial injection of adrenaline into the splenic artery could safely reduce the technical difficulty of the operation. With respect to the first two goals, both premises are true, and our study confirms the findings of Bickerstaff and Morris[8].

Good results for surgical treatment of giant splenomegaly are dependent on a team approach involving surgeon, haematologist, and anaesthetist, coupled with meticulous surgical technique. In their account of the subject, Bickerstaff and Morris[8] recommend not using adrenaline to reduce the size of the spleen, but the paper on which they base this was written in 1951. Our experience with this technique is different and, in the seven cases where it was used, the most important finding was the ease with which the operation could be performed. The 40 per cent reduction in splenic size results in the creation of a space around the spleen that improves exposure, in particular the exposure of the diaphragmatic adhesions that can present a technical challenge. The procedure was not associated with any complications aside from minor changes in blood pressure and heart rate which were not of any clinical consequence. It is impossible to estimate whether the use of adrenaline reduced the need for blood replacement, as only five of the 24 patients received intraoperative blood transfusion. However, the 40 per cent reduction in splenic volume that occurred after the adrenaline injection would have resulted in a significant autotransfusion and this is likely to have had a beneficial effect. One potential disadvantage of the procedure is that it would be inappropriate in the presence of an anaesthetic that was particularly sensitive to catecholamine injection but, in most instances, this potential problem could probably be avoided.

We have previously shown that the degree of catabolism in patients with haematological malignancy is associated with bulk of disease, with the most marked degree of catabolism occurring in patients with leukaemia and giant splenomegaly[5]. As splenectomy drastically reduces the bulk of disease in these patients it is probable that the resulting reduction in catabolism is also a factor contributing to the feeling of well-being experienced by most of these patients after surgery.

As with the other reported studies, we have shown that resection of a giant spleen is associated with a higher rate of complications than the resection of smaller spleens. Goldstone[6] points out that patients undergoing resection of a giant spleen are not only older than most other patients undergoing splenectomy, but the underlying diseases are more likely to render the patient prone to infection and/or haemorrhage. Most patients in our study had haematological malignancies known to be associated with bleeding disorders, immune defects, and catabolic metabolism[1–5]. However, despite this, there were no in-hospital deaths in our series, and of the six patients who died during the period of our study, only one did so within 1 year of operation while 21 out of 24 patients experienced either palliation of symptoms or minimization of their haematological problem.

We conclude that splenectomy plays an important part in the diagnosis of unexplained giant splenomegaly. Resection of giant spleen effectively minimizes both pressure symptoms and haematological problems, and survival is long enough to make this worthwhile. Although morbidity is comparatively high in patients undergoing resection of giant spleen most complications are minor and transient. The injection of 1 ml of adrenaline (1:10000) effects: a 40 per cent reduction of splenic volume, an autotransfusion for the patient, and greatly facilitates the ease of dissection for the surgeon.

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Right splenorenal bypass: a technical suggestion

G. Battisti, F. Stio and M. Marigliani

VI° Department of Surgery, University of Rome, Italy
Correspondence to: Dr G. Battisti

At present the most effective treatment of early renal artery stenosis is aortorenal bypass using a prosthesis or autogenous vein graft. However, this may prove impossible in patients with marked aortic arteriosclerosis and in those who have had previous surgery to the abdominal aorta. Many procedures have been suggested to solve these problems without using the abdominal aorta. They include transplantation of kidney, hepatorenal arterial bypass, gastroduodenal arterial bypass, iliorenal arterial bypass, the mesenteric–renal arterial bypass, and left splenorenal arterial bypass. It appears that use of the splenic artery for revascularization of the right renal artery has not been described in this context.

The technique involves exposure of the right renal artery after mobilization of the right side of the colon and a Kocher manoeuvre to mobilize the duodenum and head of pancreas. The splenic artery is then isolated as it runs along the upper border of the pancreas to the splenic hilum. This is achieved by opening the gastrocolic ligament, paying attention to preserving the integrity of left gastroepiploic artery. The splenic artery is encircled by a loop and dissected free until the root of the coeliac axis is reached. Bleeding from its small pancreatic branches is controlled by metal clips. The artery is then easily passed through the foramen of Winslow after full mobilization to reach the right renal artery.

After local heparinization, an end-to-side anastomosis between the mobilized splenic and the right renal arteries is made with an interrupted suture of 6-0 Prolene® (Ethicon Ltd., Edinburgh, UK, *Figure 1*). At the completion of the operation in a 67-year-old man in whom we have used this technique the spleen appeared well vascularized and we did not feel that removal was indicated. Clearly, preservation of the left gastroepiploic arcade and short gastric vessels is important in this context. The patient remains well 20 months after surgery.

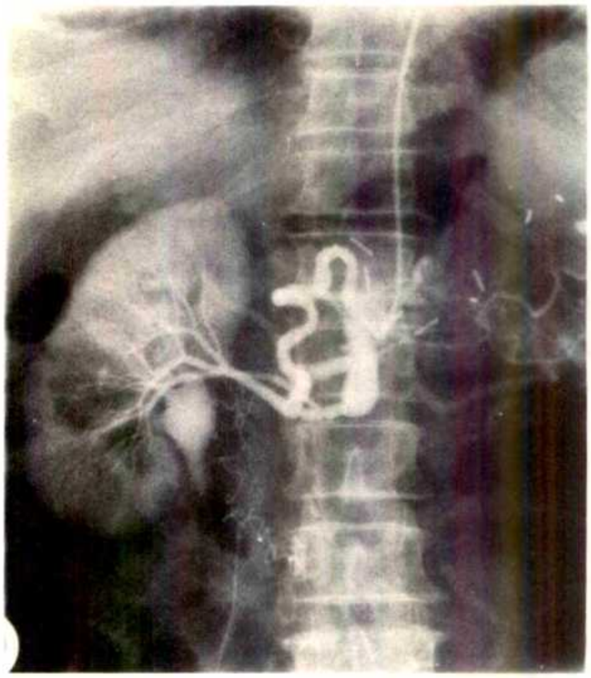

Figure 1 *Selective angiography of the splenic artery made on the seventh day after surgery showing a functioning splenorenal bypass*

We conclude that anastomosis of the splenic artery to the right renal artery may be a further useful method of bypass in renal artery stenosis where direct use of the aorta is contraindicated. Before using the splenic artery one must study its anatomy, length and calibre and ensure that it has no arteriosclerotic areas that might obviate its use.

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Surgery in patients with von Willebrand's disease

M. Blombäck, G. Johansson, H. Johnsson, J. Swedenborg and E. Wabö

Departments of Clinical Chemistry and Blood Coagulation, Medicine and Surgery, Karolinska Hospital, S-104 01 Stockholm, Sweden

Correspondence to:
Dr G. Johansson, Department of Surgery, Karolinska Hospital,
S-104 01 Stockholm, Sweden

The risk of bleeding complications in the surgical treatment of patients with von Willebrand's disease has been evaluated. Sixty-four major surgical procedures were performed in 51 patients with various forms of von Willebrand's disease. In 18 cases, the bleeding disorder was unknown at the time of surgery, resulting in bleeding complications in 12 cases (67 per cent). Forty-five operations were carried out in patients in whom the diagnosis of von Willebrand's disease was known at the time of surgery. In these patients, the following haemostatic preparations were given: factor concentrate, fresh plasma, tranexamic acid and desmopressin. Haemostatic complications occurred in three of these operations (6·7 per cent); all were managed easily. No mortality was observed. It is concluded that patients with von Willebrand's disease do not carry an increased operative risk if appropriate precautions are taken.

Keywords: Surgery, von Willebrand's disease, bleeding complications, desmopressin

Von Willebrand's disease includes a number of closely related inherited bleeding disorders[1-4]. The disease is characterized by a tendency to increased bleeding, particularly from surgical incisions and lesions of mucous membranes. This predisposition to bleeding is increased after the intake of platelet inhibitory drugs, such as aspirin. The most severe clinical manifestations include spontaneous haemarthroses and muscular haematomas. In mild cases there may be no clinical symptoms[2,4].

The biochemical defect in von Willebrand's disease is a lack of functional von Willebrand factor, a glycoprotein necessary for the adherence of platelets to exposed subendothelium. This glycoprotein is synthesized in endothelial cells and megakaryocytes, and serves as a carrier protein for factor VIII, the missing factor in haemophilia A. Thus, it promotes both the formation of a platelet haemostatic plug and the coagulation of blood at the site of an injury[4].

A bleeding disorder adds a potential risk to a surgical procedure, although modern substitution therapy should minimize this problem. To obtain further information on morbidity and mortality after major surgery in patients with von Willebrand's disease the outcome of the series of such operations has been analysed.

Patients and methods

There are about 800 patients with von Willebrand's disease who are registered at the Department of Medicine, Karolinska Hospital. In the period 1970–85, 51 underwent major surgery, that is surgical procedures with a hospital stay exceeding 24 h. The surgical procedures ranged from stripping varicose veins to laparotomies, thoracotomies and arthroplasties. The bleeding disorder was classified as severe, moderate or mild, depending on the functional activity of von Willebrand factor in plasma[5]. However, in patients who had operations before 1978, the antigen concentration of the von Willebrand factor was used for the classification[6]. The limits for the three forms were arbitrarily set at less than 5, 5–20 and 21–60 per cent, respectively. All patients with the severe and moderate forms of the disease had prolonged bleeding times. If the bleeding disorder was known of before surgery, prophylactic therapy was given. Treatment was adjusted according to the intended surgical procedure and the seriousness of the von Willebrand's disease, and included the administration of factor concentrate, fresh plasma, desmopressin acetate and tranexamic acid. The contraindication of platelet inhibitors was stressed. The year of operation had an influence on the haemostatic therapy. Thus, during the latter years of the study, more patients were treated with desmopressin acetate than with plasma products.

Appropriate information was collected from the records at hospitals or clinics where the operations were performed. In total, 37 clinics at 20 different hospitals in Sweden, mostly in the Stockholm area, were involved. All records were re-evaluated with respect to classification, haemostatic treatment and bleeding complications.

Results

Disease unknown at operation

Sixteen patients (5 men, 11 women) underwent 18 surgical procedures without the knowledge of the presence of the bleeding disorder. One patient had neglected to give an adequate history of his disease. In the other cases, the diagnosis had not yet been made. The mean age of the patients was 32 years (range 16–46 years). *Table 1* summarizes the results. No mortality was observed. Bleeding complications were observed in 12 patients (67 per cent of surgical procedures): in eight patients there was abnormal oozing either during the operation or in the immediate postoperative period; in four patients large haematomas occurred a few days after operation. Two patients had a reoperation for postoperative bleeding. The haemostatic problem usually required the administration of fresh whole blood, or fresh plasma; in all but one case, further investigation of the coagulopathy was initiated. In the latter case, as in all the other patients without bleeding complications while in hospital, the diagnosis of von Willebrand's disease was made later.

Disease known at operation

Thirty-five patients (13 men, 22 women) were operated on with the diagnosis of von Willebrand's disease having been made preoperatively. *Table 2* summarizes the essential information of these operations. Forty-five various major operations were performed. The mean age of the patients was 35 years (range

Table 1 *Surgical procedures in patients in whom von Willebrand's disease was undiagnosed at operation*

Form	Surgical procedures (*n*)	Haemostatic complications (*n*)
Mild	13	9
Moderate	4	2
Severe	1	1
Total	18	12

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Table 2 *Surgical procedures in patients with von Willebrand's disease known before operation*

Form	Surgical procedures (*n*)	Haemostatic complications (*n*)
Mild	25	2
Moderate	16	1
Severe	4	0
Total	45	3

5–65 years). There was no operative mortality, and no patient required reoperation for bleeding. In three patients, haemostatic problems were observed, giving an incidence of complications for treated patients of 6·7 per cent.

Discussion

The prevalence of the severe form of von Willebrand's disease is less than 0·001 per cent of the Swedish population. Most patients having this form are known, and have been diagnosed after family screening, or after an episode of abnormal bleeding. In contrast, the heterozygotes with mild forms constitute a significant part of the population. As many of them have not been diagnosed the true prevalence is difficult to establish. Furthermore, even with appropriate analytical methods, conclusive diagnostic evidence is difficult to obtain in some of these cases[7]. The disease is inherited in an autosomal manner, either dominant or recessive[2-4]. Knowledge of its clinical penetrance, together with population and genetic statistics, suggests a prevalence in Sweden of approximately 1 per cent.

In undiagnosed cases of von Willebrand's disease, a careful preoperative history, even in mild forms, often indicates a coagulation disorder, which initiates further evaluation of the haemostatic function. However, there are always patients in whom the diagnosis of von Willebrand's disease has not been made before surgery. In 1973, Silwer reported that surgical procedures in such cases often resulted in severe bleeding complications, sometimes fatal[8]. In the present report the number of complications was approximately the same. However, the clinical outcome of the complications in our study was benign, probably due to improved therapy. Accordingly, abnormal bleeding initiates the transfusion of fresh plasma. Concomitantly, appropriate tests for evaluation of a possible coagulopathy are performed.

Preoperative diagnosis of the bleeding disorder is mandatory in order to prevent bleeding complications. This report demonstrates that the number of bleeding complications in patients in whom von Willebrand's disease was known before surgery was about the same as in patients with normal haemostasis[9]. In fact, none of these bleeding episodes prompted reoperative surgery. This corroborates previous findings by Larsson[10].

The Stockholm area has a population of 1·5 million, and about 100 000 major operations are performed every year (6·7 per cent). The corresponding incidence in patients with von Willebrand's disease registered at this hospital was about the same, i.e. 8 per cent. It has been suggested that the bleeding from mucosal membranes in patients with von Willebrand's disease would result in a significant increase in the number of surgical procedures, especially in the stomach and duodenum[11]. The present study does not support this hypothesis. In fact, very few of the operations were performed because of complications from the bleeding disorder *per se*; there was no difference in the type of surgical procedure performed compared with the corresponding figure in the average population.

In patients with von Willebrand's disease, efficient substitution therapy is easily achieved with factor concentrate. On account of the risks with plasma concentrate, desmopressin is an attractive alternative. It is a synthetic analogue of vasopressin which increases the plasma concentration of the factor VIII—von Willebrand factor complex—thus normalizing the haemostatic defect[12-14]. The experiences reported in surgical patients have been encouraging[15-20]. Because of its recent introduction, only a small number of surgical procedures were carried out after treatment with desmopressin. All these operations were completed without bleeding complications, as has been the case in other recent reports[15-20], a fact which favours the continued use of this drug in patients with von Willebrand's disease.

Surgical risk is similar to normal in patients with von Willebrand's disease. The preferred prophylaxis includes tranexamic acid. In patients with mild forms of von Willebrand's disease desmopressin is preferable to plasma products. In the severe form, the megakaryocytes and endothelial cells are not capable of synthesizing von Willebrand factor[13] and consequently, in such patients, and in subjects synthesizing abnormal molecular forms of von Willebrand factor, desmopressin is not appropriate for prophylactic therapy and should be replaced by plasma products[21]. Furthermore, in those patients, immediate access to an experienced coagulation laboratory is essential especially when extensive surgical procedures are scheduled.

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Surgical workshop

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Use of deep tension sutures and buttress plates for frequent relaparotomy

M. R. J. Lansdown and M. J. McMahon

University Department of Surgery, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, UK
Correspondence to: Mr M. R. J. Lansdown

After laparotomy and débridement of complex intra-abdominal abscesses, the use of gauze packs and frequent relaparotomy has been suggested as an alternative to tube drainage. An abdominal 'zip fastener' or polypropylene mesh has been used to facilitate relaparotomy, but when sepsis has subsided the wound is ultimately left open and allowed to granulate. As a consequence, myocutaneous flaps or skin grafts are sometimes necessary to obtain skin cover and a cosmetically acceptable result. In our experience, a wound closure system that utilizes buttress plates and plastic-coated wire sutures (Ventrofil®, B. Braun Ltd., Aylesbury, UK) greatly facilitates relaparotomy and can lead to an acceptable final wound that does not require surgical reconstruction.

For upper abdominal abscesses a transverse or 'roof-top' incision is our preferred incision when relaparotomy is likely because the tendency to gape is less than with a vertical incision. Necrotic tissue and pus are removed. Areas destined for reinspection at further laparotomy are lined with non-adherent gauze. The incision is then closed, or partially closed if there is tension when approximating the wound edges, using the Ventrofil buttressed closure system. Up to four pairs of buttresses may be required for a wide 'roof-top' incision. The polypropylene-coated braided wire sutures are placed as a horizontal mattress through all layers of the abdominal wall except the peritoneum, about 3 cm from the edges of the wound (*Figure 1*). Using traction on the sutures the wound is closed to the appropriate degree. Care is taken to ensure that viscera are not trapped between the sutures. It is important that the ends of the sutures are left long after the knots have been tied (*Figure 2*). The design of the buttress plate allows adjustment of suture tension postoperatively without the need to retie the knots, by moving the suture to a different notch in the buttress. The wound can be covered with a loose absorbent dressing or left open to the air.

At relaparotomy the plates are removed and the abdomen is prepared. The knots are easily untied because of the plastic coating, and the free ends of the sutures, which were left long, are secured with artery forceps while relaparotomy is carried out. We have found that there is ample room between the sutures to carry out full inspection, further débridement and repacking. During the procedure, the plates are soaked in aqueous povidone-iodine solution, and the wound is then closed as before. The procedure is repeated until further laparotomy is not needed, and then the buttressed closure is left *in situ* for 4 weeks to allow healing of the fascial layers and to prevent incisional herniation.

This method of wound closure is convenient to use and allows frequent relaparotomy without the need to place new sutures each time.

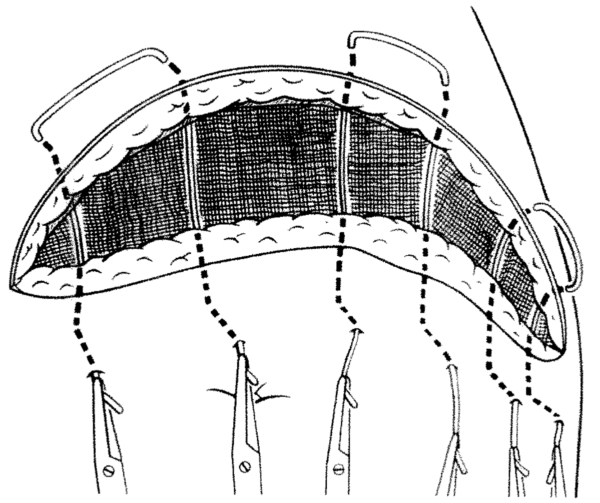

Figure 1 *Correct placement of sutures after insertion of abdominal pack*

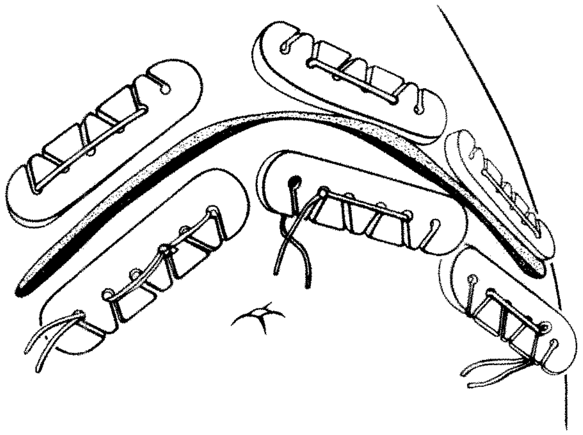

Figure 2 *Wound closure using buttress plates*

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Plasma eicosanoids, platelet function and cold sensitivity

D. Wilkinson, P. Vowden, L. Gilks*, A. B. Latif†, S. M. Rajah* and R. C. Kester

*Department of Vascular Surgery, St. James's University and Seacroft Hospitals, *Department of Haematology, Seacroft Hospital and †Cardiac Research Laboratory, Killingbeck Hospital, Leeds, UK*

Correspondence to:
Dr D. Wilkinson, Department of Vascular Surgery, St. James's University Hospital, Beckett Street, Leeds LS9 7TF, UK

As abnormal eicosanoid (prostaglandin) metabolism has been suggested as a factor in the aetiology of vasospastic diseases we have measured levels of stable eicosanoid metabolites using a radioimmunoassay in 30 normal subjects and 31 patients with Raynaud's phenomenon. There were 13 patients with primary Raynaud's, ten with Raynaud's secondary to scleroderma and eight men with vibration white finger (VWF) disease. We have also measured platelet aggregation to adenosine diphosphate (ADP), collagen and adrenaline in 19 normal subjects, 22 patients with primary Raynaud's, 12 with Raynaud's secondary to scleroderma and 14 men with VWF. When compared with our normal subjects, patients with VWF have an elevated thromboxane B_2 level, with a normal 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) level. Their platelets are less sensitive to ADP and collagen. Patients with primary and secondary Raynaud's have elevated thromboxane B_2 levels but this is much more marked in the secondary group. Patients with primary Raynaud's have a normal 6-keto-$PGF_{1\alpha}$ level but in patients with secondary Raynaud's the 6-keto-$PGF_{1\alpha}$ level is markedly raised. The platelets from both groups are more sensitive to ADP and collagen and this is more marked in the secondary group. Whether these phenomena are a cause or an effect of vasospasm remains unknown.

Keywords: Raynaud's, eicosanoid levels, prostacyclin, platelet aggregation

Despite many theories[1] the pathophysiology of Raynaud's phenomenon remains unknown. Recent interest has centred on the possible role of eicosanoids (prostaglandins)[2]. Prostacyclin[3] is a vasodilator that inhibits platelet aggregation; thromboxane A_2 is a vasoconstrictor that induces platelet aggregation. These eicosanoids represent opposite poles of a homeostatic mechanism, an alteration of the balance in favour of thromboxane could produce vasoconstriction and alter platelet behaviour.

Controversy exists regarding what is a 'normal' plasma prostanoid level and this is paralleled by the findings in specific disease states. Several workers have found elevated prostacyclin and thromboxane stable metabolite levels in patients with Raynaud's phenomenon when compared with controls, both in plasma[4–6] and in urine[7].

If normal metabolite levels represent a real difference in circulating parent prostaglandin levels then altered platelet behaviour might be expected. There have been few studies and again there is a lack of consensus. Most work has compared platelet aggregation using the techniques of Born[8] and found that the platelets from patients with Raynaud's phenomenon are more sensitive than those from controls[7,9]. There have been no satisfactory studies of patients with vibration white finger (VWF) disease.

The aim of this study was to clarify the situation regarding eicosanoid levels and platelet behaviour. We have measured plasma thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) levels in a series of controls and patients with Raynaud's phenomenon. We have also compared the ratio between the two metabolites with patient diagnosis and *in vitro* platelet behaviour.

Patients and methods

Patients

Eicosanoid levels were measured in 61 subjects, and platelet aggregation studies carried out in 67 subjects. The two parts of the study were carried out at different times; although many subjects participated in both studies, the results for individuals cannot be directly compared.

Subjects suffering from Raynaud's phenomenon have been divided into groups on the basis of a clinical, haematological and immunological assessment. The age and sex distribution of the groups are given in *Table 1*. Six of the normal females in whom we measured eicosanoid levels were menstruating. Their results have been analysed separately because of the known small, cyclical changes in physiological temperature regulation[10]. In the secondary Raynaud's group, one patient has a vasculitis of uncertain aetiology, all the others have scleroderma. The men with industrial VWF disease have all had the disease for at least 2 years and were graded between one and four on the Taylor–Pelmear[11] scale. Most were graded three or four and either were grinders, swagers or operated pneumatic hand-held road breakers.

Eicosanoid measurements

Blood samples were taken at 08.00 hours, after 30 min quiet bed rest, and added to ethylenediaminetetra-acetic acid (EDTA) 1·5 mg/ml of whole blood and 0·9 ml of 40 per cent aspirin solution. The samples were immediately centrifuged at 1000*g* for 20 min, platelet free plasma was frozen at −25°C for later batch assay.

After solid phase extraction using an octa-diocyl-silene column, the eicosanoid fraction was eluted into methyl formate, evaporated and then purified using high performance liquid chromatography. The metabolites were collected and concentrated by freeze drying. Thromboxane B_2 and 6-keto-$PGF_{1\alpha}$ levels were measured using a radioimmunoassay technique.

Platelet aggregation measurements

Venous blood was added to citrate, centrifuged at 200*g* for 10 min, and platelet rich plasma was removed. The residue was respun at 1000*g* for 20 min to yield platelet poor plasma. By diluting the platelet rich plasma with platelet poor plasma, plasma with a platelet count of 250×10^9/litre was obtained which was used for all aggregation studies. They were carried out using a Chrono-log dual channel aggregometer (Chrono-log Corporation, Havertown, USA) and three aggregating agents; two concentrations of collagen, 2 and 4 mg/l; six serial dilutions of ADP: 10, 5, 2·5, 1·25, 0·625 and 0·3125 μM; and finally a single concentration of adrenaline, 5 μM.

Following the addition of an aggregant platelets undergo a shape change and then aggregate into large clumps rendering the plasma increasingly transparent. A platelet aggregation curve is a recording of

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Table 1 *Age and sex distribution of the subjects included in the study*

	Eicosanoid levels			Platelet aggregation		
	Men	Women	Mean age (range)	Men	Women	Mean age (range)
Normals	11	19 (6*)	32 (18–68)	9	10	28 (18–52)
Primary Raynaud's	6	7	30 (17–69)	6	16	33 (17–69)
Secondary Raynaud's	1	9	42 (24–63)	2	10	40 (24–63)
VWF	8	0	38 (24–52)	14	0	34 (24–64)

* Number of menstruating women; VWF, vibration white finger disease

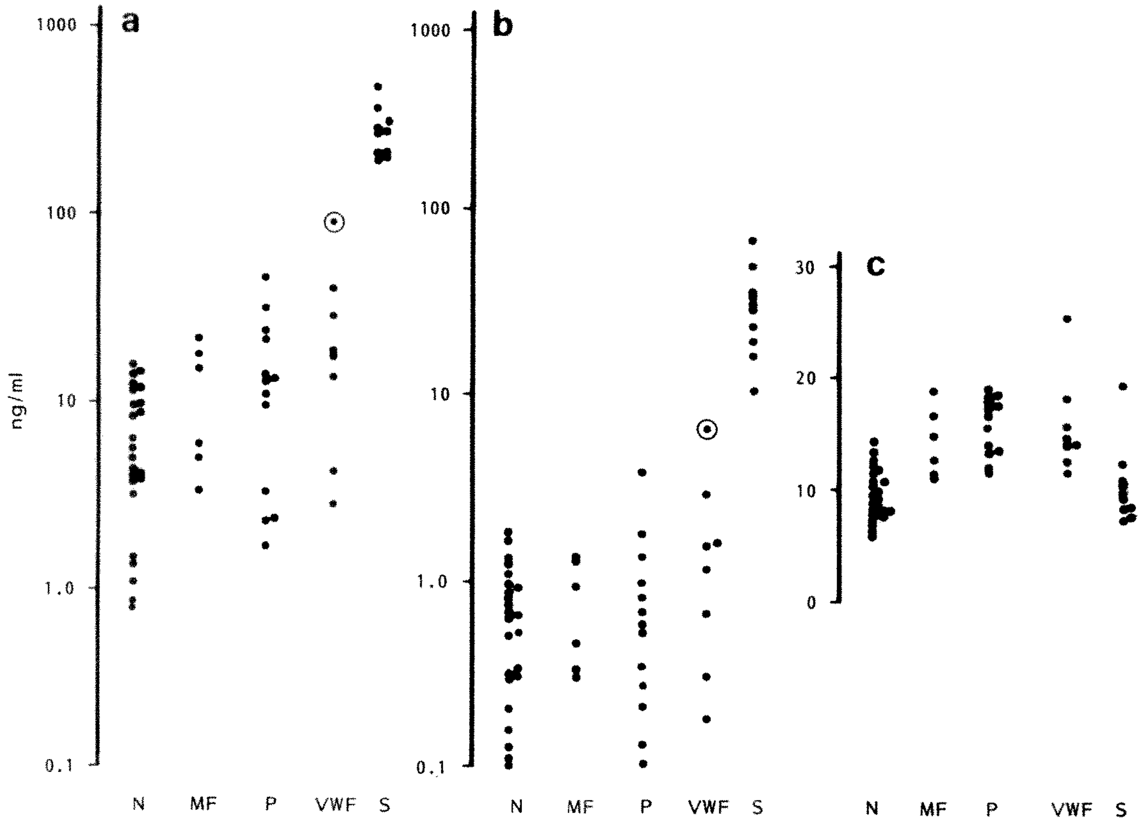

Figure 1 **a** *Thromboxane B_2*, **b** *6-keto-prostaglandin $F_{1\alpha}$ levels*, **c** *the ratio of plasma thromboxane B_2: 6-keto-prostaglandin $F_{1\alpha}$ in the diagnostic groups: N, normal subjects; MF, menstruating females; P, subjects with primary Raynaud's; S, subjects with secondary Raynaud's; VWF, men with vibration white finger.* ⊙, *One patient subsequently found to have a circulating autoantibody was removed from the VWF group before analysis of results*

light transmission against time; steep curves with large heights represent a greater platelet sensitivity to the aggregant.

For each ADP curve, the angle, the height after 3 min and the maximum height has been recorded. The highest dose of ADP at which aggregation failed to occur has also been noted. For each collagen curve we have measured the duration of the delay before aggregation in seconds (lag phase), the angle, the height after 3 min and the maximum height. For adrenaline we have measured the height of the curves at 3 and 5 min.

All results are expressed as medians with 5 and 95 percentiles. Statistical analysis is by the Mann–Whitney *U* test, results are considered highly significant when $P < 0{\cdot}001$ and significant when $P < 0{\cdot}05$.

Results

Eicosanoid metabolite levels

The plasma thromboxane B_2 and 6-keto-PGF$_{1\alpha}$ levels for each of the diagnostic categories is given in *Figure 1*.

With regard to 6-keto-PGF$_{1\alpha}$, the median result in our normal population was 0·68 ng/ml. There was no correlation between the levels obtained and age, sex or smoking habits. The median level found in patients with secondary Raynaud's was 29 ng/ml. This was highly significantly elevated when compared with each of the other diagnostic groups. Within the secondary Raynaud's group the level did not vary with the duration or activity of the disease. There were no significant differences between the levels obtained in any of the other groups.

With regard to thromboxane B_2, the median result in our normal population was 5·8 ng/ml. Again the levels bore no relationship to age, sex or smoking habits. The median level found in patients with secondary Raynaud's was 280 ng/ml. This was highly significantly elevated from those values obtained in our normal population. Again the level did not vary with the duration or activity of the disease process. In addition, the levels obtained in patients with primary Raynaud's and VWF were both significantly elevated from our normal values, although the magnitude of this increase was considerably less than that found in patients with secondary Raynaud's. The median levels found in primary Raynaud's and VWF were very similar, at 12·5 and 17·3 ng/ml. There was no significant difference in the levels obtained in our small group of menstruating women, 14·9 ng/ml, when compared with our other normal subjects.

We have also compared the ratio of the two metabolites. There is no significant difference between the ratio in patients with secondary Raynaud's and the ratio obtained in our normal population. Despite the very high levels of both metabolites in this patient group the median ratios were very similar to those of the normal group, 9·41 and 9·60. In each of the other three groups, patients with primary Raynaud's or VWF and menstruating women, the ratio was significantly elevated in favour of thromboxane B_2.

It is interesting to note that one patient who was originally classified in the VWF group had very high levels of both metabolites, well above the other members of that group. He has subsequently been shown to have a circulating autoantibody and probably has scleroderma. This patient was removed from the VWF group before the analysis of the results.

Platelet aggregation

ADP. Lower doses of ADP were more discriminating between the groups; *Figure 2* shows the extent of aggregation after 3 min for three doses of ADP.

At 2·5 μM ADP, the responses of platelets from normal subjects, patients with primary Raynaud's and patients with secondary Raynaud's were no different with medians all around 50 per cent. The platelets from patients with VWF were significantly less sensitive to this dose of aggregant with a median extent of aggregation of only 34 per cent.

At 1·25 μM ADP, platelets from patients with VWF were highly significantly less sensitive to the aggregant than the normal group. The median extents of aggregation were 12 and 21 per cent respectively. In contrast, at this concentration of ADP, platelets from patients with primary Raynaud's were significantly more sensitive to the aggregant, with a median extent of aggregation of 35 per cent. This trend was even more marked for patients with secondary Raynaud's, with a median extent of aggregation of 52 per cent.

At 0·625 μM ADP, platelets from normal subjects and patients with VWF showed very little response to the aggregant and there was no difference between them. Again patients with primary and secondary Raynaud's showed a highly significantly more marked response to this concentration of aggregant, with median extends of aggregation of 11 and 16 per cent respectively.

In each case the maximum height that the curve achieved reflected very closely the height at 3 min and analysing these results did not add anything to the analysis of the 3 min results. The angle of the steepest part of the curve was an unhelpful measurement, it is imprecise and did not even reliably distinguish the concentration of aggregant used.

Another way of expressing platelet sensitivity to ADP is to find the highest concentration at which aggregation failed to occur. In our normal population this was most commonly 1·25 μM, for patients with VWF the results were very similar. However a significantly lower concentration of ADP was needed before platelets from patients with primary Raynaud's failed to aggregate. The most common concentration needed was 0·625 μM. This trend was even more marked in patients with secondary Raynaud's in whom a concentration of 0·3125 μM was most commonly needed before their platelets failed to aggregate.

Collagen. Measurement of the height of the collagen curve did not reveal any differences between the patient groups but there were differences in the duration of the delay before the onset of aggregation (lag phase). The lag phases in seconds for the 2 mg/l collagen curves are given in *Figure 3*.

At 4 mg/l there were only small differences between the groups although the results reflected the findings using ADP. The median lag phase for platelets from patients with VWF was 77 s, which was slightly longer than that found in the normal subjects, 58 s, but the difference was not significant. The median lag phases for platelets from patients with primary and secondary Raynaud's were 50 and 48 s respectively. These were shorter than that found for the normals and the difference reached significance for the primary group.

The lower of our two collagen concentrations, 2 mg/l, produced a better separation between the groups (*Figure 3*). The median lag phase in our normal subjects was 82 s. Again, although the lag phase for platelets from patients with VWF was longer than this, with a median of 96 s, the difference was not significant. Patients with primary and secondary Raynaud's both had shorter lag phases than the normals, median values were 72 and 61 s respectively. In both cases the difference was significant.

Adrenaline. Adrenaline was an unhelpful aggregating agent, producing a very variable response with no distinction between the groups.

Discussion

As the half-lives of prostacyclin and thromboxane A_2 are extremely short their levels are often inferred by measurement of their stable metabolites, usually 6-keto-PGF$_{1\alpha}$ and thromboxane B_2 respectively.

Absolute levels of 6-keto-PGF$_{1\alpha}$ are best obtained by gas chromotography–mass spectrometry but it is expensive and cannot cope with large numbers of samples[12]. Belch suggests that radioimmunoassay[13,14] is probably the best method for

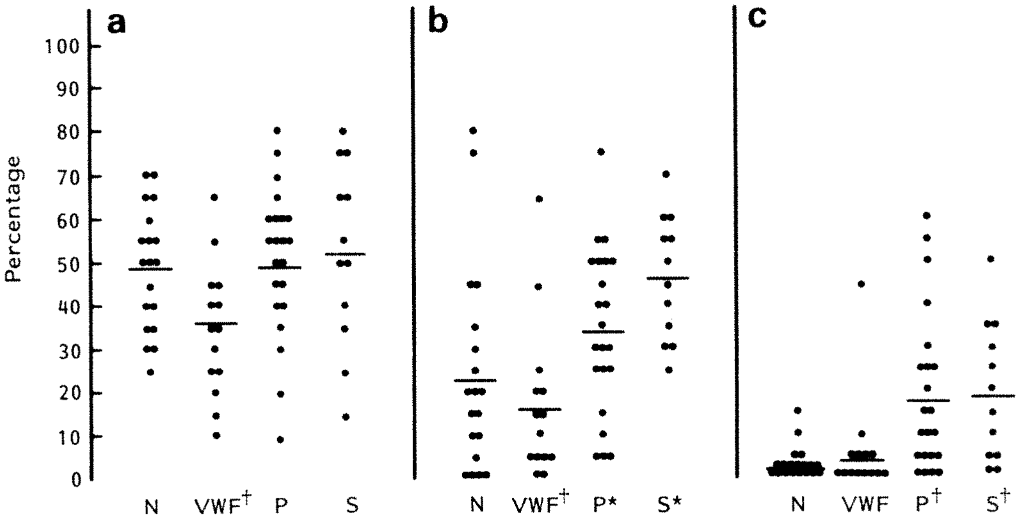

Figure 2 *Extent of aggregation after 3 min (%) to* **a** *2·5 μM,* **b** *1·25 μM and* **c** *0·625 μM three doses of ADP. N, normal subjects; VWF, men with vibration white finger; P, subjects with primary Raynaud's; S, subjects with secondary Raynaud's; * significantly different from normal, $P<0·05$; † highly significantly different from normal, $P<0·001$ (Mann–Whitney U test)*

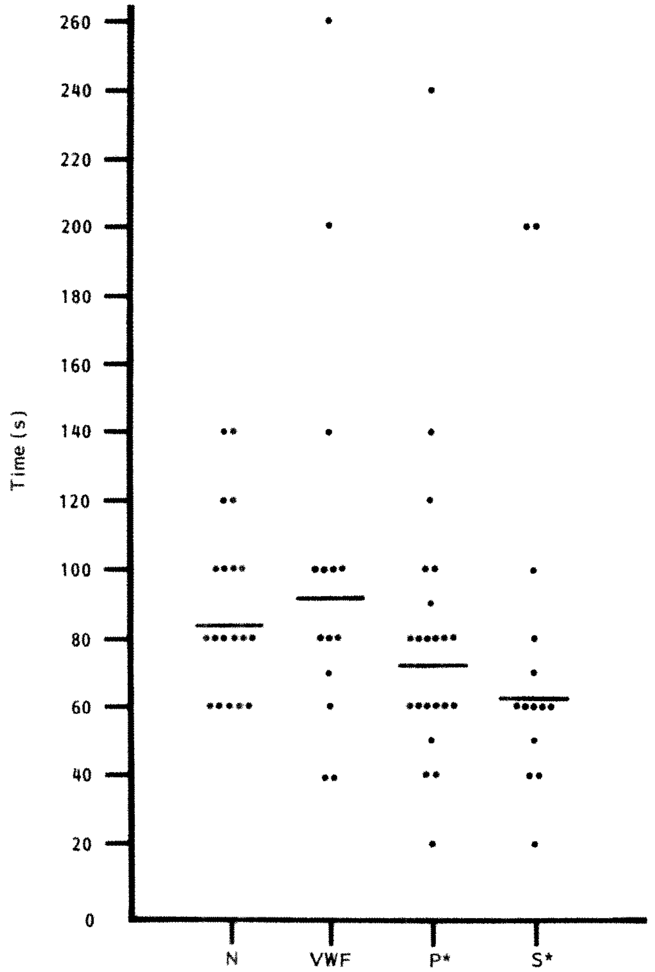

Figure 3 *Duration of the collagen lag phase in seconds (2 mg/l). N, normal subjects; VWF, men with vibration white finger; P, subjects with primary Raynaud's; S, subjects with secondary Raynaud's; * significantly different from normal,* $P<0{\cdot}05$

measuring prostacyclin metabolites in plasma as it is possible to reach a high sensitivity, with good precision and accuracy.

From amongst the controversy regarding the most appropriate measurement technique, and the conflicting results, some consensus regarding methodology has gradually emerged[15–17]. A resting period of 30 min before blood sampling avoids the possibility of raised levels due to psychological stress and physical activity. EDTA or citrate are preferred anticoagulants; heparin should not be used. Traumatic venepuncture is more likely to affect the results than a short period of venous occlusion, although this should be kept as brief as possible. Sample processing at 4°C is useful but if the sample is centrifuged immediately this is not so important. There is likely to be a non-specific increase in the values if the samples are stored for longer than 2 weeks but this effect can be reduced by storage at −70°C rather than −20°C. Repeated freezing and thawing clearly increases immunoreactive material.

These precautions have been carefully followed. The only deviation is that our storage temperature was too high. This may explain the high level of our results when they are compared with the findings of others, but for the purposes of this study we are more interested in a comparison between our patient groups. As all the samples were stored in the same manner a valid comparison between the results can be made but the absolute levels are almost certainly unreliable. It is important to realize that it is impossible to measure resting plasma eicosanoids, as the procedure of venesection and sample processing is bound to raise the levels, despite all precautions. In reality we have performed an eicosanoid 'stress test'.

The finding of high metabolite levels with a normal ratio in patients with secondary Raynaud's cannot be explained but perhaps indicates a fundamental disturbance in prostaglandin metabolism. An increase in the thromboxane metabolite in the other patient groups, without an increase in the prostacyclin metabolite, again cannot be explained. It is unlikely to be secondary to a vasospastic attack as care was taken to obtain all blood samples after an equilibration period in a warm environment.

The platelet results are also difficult to explain. Unfortunately in some studies no distinction has been made between patients with idiopathic Raynaud's phenomenon and Raynaud's syndrome secondary to a connective tissue disorder[18,19] so there is little previous work with which to compare our results directly. This is particularly true for the most surprising of our findings, in patients with VWF. Ikehata[20] found increased sensitivity to a range of aggregating agents in a series of patients with VWF, but these patients included some who suffered from a number of other diseases including peripheral vascular disease whilst the control group only contained healthy subjects. Bovenzi[21] found no abnormalities in platelet function or blood clotting parameters in 22 vibration-exposed foundry workers but only one subject was graded as one on the Taylor–Pelmear scale[11], all the others were graded zero.

When compared with our normal subjects, patients with VWF have an elevated thromboxane B_2 level, with a normal 6-keto-$PGF_{1\alpha}$ level. Their platelets are somewhat surprisingly less sensitive to ADP and collagen. Patients with primary and secondary Raynaud's have elevated thromboxane B_2 levels but this is much more marked in the secondary group. Patients with primary Raynaud's have a normal 6-keto-$PGF_{1\alpha}$ level but in patients with secondary Raynaud's the 6-keto-$PGF_{1\alpha}$ level is also markedly raised. The platelets from both groups are more sensitive to ADP and collagen and this is more marked in the secondary group.

A simple link between elevated thromboxane levels and increased platelet sensitivity is unlikely in view of the diminished response of platelets from patients with VWF to both aggregating agents, especially ADP.

To conclude, we have demonstrated abnormal eicosanoid levels and *in vitro* platelet behaviour in patients with Raynaud's phenomenon. The relationship between these two phenomena is unclear. Platelets both produce eicosanoids and have their function regulated by them. It is therefore impossible to determine if the abnormalities we have demonstrated in platelet behaviour are a cause or an effect of vasospasm.

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Out-patient operation of inguinal hernia in children

S. Mejdahl, H. J. Gyrtrup and E. Kvist

Paediatric Section, Department of Surgery, Sundby Hospital, DK-2300 Copenhagen S, Denmark

Correspondence to:
Dr H. J. Gyrtrup, Vejrøgade 6, 2,
DK-2100 Copenhagen Ø, Denmark

A retrospective review is presented of 496 children with a median age of 4 years (range 0–13 years) on whom a total of 527 hernia repairs were performed as out-patients. No wound infections were observed, and the rate of early surgical complications was 1·5 per cent. There were 15 (3·7 per cent) known recurrences. No complications from the anaesthetic were recorded. Owing to the negligible infection rate and the low surgical complication and recurrence rates it is concluded that children with inguinal hernia would benefit from operation as out-patients, and that they should be operated on immediately after diagnosis, irrespective of age. Besides probably minimizing the children's psychological trauma, out-patient surgery provided considerable savings to the health service in the present study.

Keywords: Inguinal hernia, herniotomy, out-patient

The tendency over the past few years has been for out-patient surgery for children wherever possible, the child's admittance period thus being shortened and psychological trauma minimized. Additionally, out-patient surgery may contribute to the curbing of rising costs of health services[1–5].

Since 1980, all herniotomies performed on children at Sundby Hospital have been out-patient procedures performed immediately after diagnosis, irrespective of age.

In the present review, we have assessed the results of these operations to ascertain whether out-patient surgery in this form is surgically and anaesthesiologically justifiable.

Patients and methods

In the period from 1 January 1980 to 31 December 1987, out-patient operation of inguinal hernia was performed on 496 consecutive children with a median age of 4 years (range 0–13 years). Thirty-one children had bilateral hernia, so that 527 hernia repairs were carried out. Sixteen children are included twice, owing to operation for right-sided and left-sided inguinal hernia at different intervals. Age grouping is indicated in *Figure 1* and sex ratio and side presentation are given in *Table 1*.

On the morning of admission, patients were premedicated rectally before being moved to the operating theatre. Anaesthesia was produced with halothane, by face mask; endotracheal anaesthesia was practised only in cases of bilateral hernia. The skin was disinfected twice with 0·05 per cent chlorhexidine solution. Operation was performed by either the department's senior surgeon or a surgical registrar. In all cases, the skin was closed intracutaneously with soft-catgut-plain (B. Braun, Melsungen, FRG). None of the patients received peroperative antibiotic treatment. On full awakening from anaesthesia patients were examined by a paediatrician and discharged with notice to attend the out-patient clinic a week later.

A total of 462 patients representing 508 hernia repairs could be traced. The parents of these patients were sent a questionnaire asking whether the child had undergone a second operation for recurrence of the hernia and whether there had been any other problems regarding the wound. The questionnaire was returned by 366 parents (79·2 per cent), representing 402 hernia repairs (76·3 per cent).

Results

One patient contracted a lesion of the bladder and was admitted for a period of 5 days. One patient developed a scrotal haematoma requiring evacuation, admittance thus being prolonged for 4 days. Nineteen patients remained for a single night: eight of these on sociological grounds, six due to vomiting, three on account of bloody seepage from the wound and a further two with slight temperatures. Three patients were readmitted and reoperated on after 1 day, two of these because of wound haematoma, and the third because of sustained external bleeding. In three patients, the scheduled examination the following week showed minor scrotal haematomas that did not require treatment. No wound infections or scrotal abscesses were observed. According to the hospital records and the questionnaires, no late infections or other wound problems were recorded. The questionnaires revealed 12 recurrences (3·0 per cent) equally distributed among the age groups. From the hospital records another three recurrences were found. The recurrence rate on 406 hernia repairs was thus 3·7 per cent.

Discussion

In terms of age, sex and side of presentation of the hernias, our findings correspond with those of investigations of in-patient

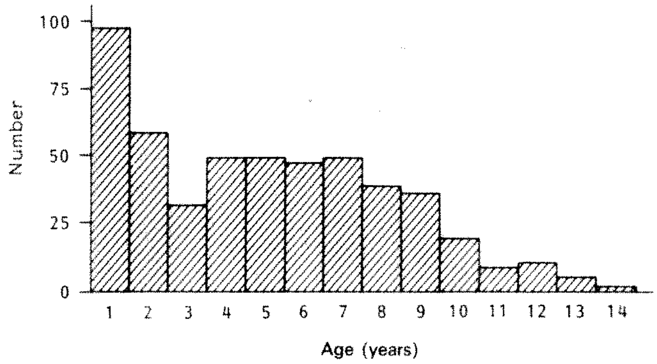

Figure 1 *Number of children treated for inguinal hernia in age groups: 0–1 years, >1–2 years etc. up to >13–14 years*

Table 1 *The side of presentation and sex ratio of 496 children with inguinal hernia*

	Side of presentation			
	Right	Left	Bilateral	Total
Boys	246 (63·9)	124 (32·2)	15 (3·9)	385 (77·6)
Girls	67 (60·4)	28 (25·2)	16 (14·4)	111 (22·4)
Total	313 (63·1)	152 (30·6)	31 (6·2)	496

Values in parentheses are percentages

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herniotomy; this also applies to the incidence of bilateral hernia in girls, which is significantly higher than in boys ($P<0{\cdot}0005$)[3,6,7]. Five cases of immediate surgical complications that required treatment occurred, and a further three cases required observation. This gives a surgical complication rate of 1·5 per cent, which also corresponds with other findings. The recurrence rate is no different from that in other studies[3,6–8]. However, as indicated in the results above, none of the patients suffered from postoperative wound infection, which contrasts with in-patient herniotomy of children, where the incidence of infection is recorded as 2·3 per cent[7].

A factor of possible major importance for the negligible incidence of infection in the present study may be that patients were operated on immediately after admittance and discharged on the same day; the possibility of nosocomial infection under these circumstances is assumed to be slight[1,9]. This does not, however, explain why children in nappies, with the possibility of massive faecal fouling of the wound, avoid infection. Better subcutaneous perfusion, and thereby higher tissue oxygen tension, in children could be considered as a possible influencing factor[10,11]. As shown, all the wounds were closed intracutaneously with soft-catgut-plain; this type of suture is possibly less of a tissue irritant than others. Under all circumstances, with intracutaneous technique, skin perforations are avoided and a possible gateway for bacteria is thus excluded. Also of relevance to the low complication rate in the present series is the fact that the operations were performed by experienced surgeons[12].

In conclusion, our results seem to indicate that otherwise healthy children with inguinal hernia can be recommended for out-patient surgery. As there are no differences in wound infection and surgical complication rates between the smallest and the oldest children, and bearing in mind the greater risk of hernial incarceration in the smallest children[8,13], we advise that the herniotomy should be performed as soon as possible after diagnosis. In addition to the probable minimization of the children's psychological trauma, the economic saving was approximately 2·5 million Danish kroner (about £300 000 sterling) in the present series.

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Use of the ultrasonic aspirator in splenic preservation

C. P. Nnochiri, M. Rees and R. J. Heald

Department of Surgery, Basingstoke District Hospital, Basingstoke, Hampshire RG24 9NA, UK
Correspondence to: Mr M. Rees

Conservation of splenic function is now generally regarded as a desirable objective in the management of splenic injury or disease[1]. Attempts to preserve a viable splenic remnant have led to various techniques that testify to surgical ingenuity[2–4]. Two cases of hemisplenectomy using the ultrasonic surgical aspirator are presented.

Case reports

Case 1

A 10-year-old boy presented with upper abdominal pain and a mass in the left upper quadrant. Ultrasound examination confirmed a cyst in the lower part of the spleen, with a normal blood picture. The patient's abdominal tenderness led to a semiurgent laparotomy, at which time a partial splenectomy was performed using the ultrasonic aspirator to remove the cyst intact. Blood loss was less than 100 ml and the patient's recovery was uncomplicated.

Case 2

A 34-year-old man was referred with upper abdominal pain and distension. No haemopoietic disorder was found, but ultrasound scanning showed a cyst in the spleen, confirmed by a computed tomography (CT) scan to measure 16 cm. The ultrasonic aspirator was used to perform a partial splenectomy to excise the cyst intact. Blood loss was less than 400 ml and the patient's recovery was smooth except for transient left basal atelectasis.

Technique

After a midline (case 1) or a left subcostal (case 2) incision, the spleen was completely mobilized and its vascular pedicle clearly dissected. Intraoperative ultrasound helped to delineate the cyst margin. The segmental arterial branches were ligated and, after demarcation, the splenic capsule was incised with diathermy. The ultrasonic aspirator was then used to dissect the splenic parenchyma (*Figure 1*), skeletonizing the vessels for easy haemostasis by diathermy and ligation. In the second case, one oozing vessel was stopped by clamping the splenic artery and applying collagen fleece to the raw surface for 5 min.

Discussion

Ultrasonic dissection is well established in neurosurgery and hepatic surgery. Two groups in the USA have recently developed the technique of ultrasonic splenic dissection[5–7]. We wish to support this work by advocating ultrasonic partial splenectomy as a means of preserving splenic tissue.

The essential feature of the Cavitron® ultrasonic surgical aspirator (Sigmacon UK Ltd., UK) used in these cases is a pencil-like, hand-held device whose tip vibrates at high frequency. The hollow tip has continuous suction and an irrigation channel to keep the tip clean throughout. Vibration at the target tissues causes vacuolation and cavitation of nearby cells. The fragmentation of cells is proportional to their water content. The hepatic, splenic and neural tissues are most susceptible, while tissues having a high content of collagen and elastin are relatively protected, except at high power. In this way, blood vessels, bile ducts etc. can be skeletonized as the surrounding parenchyma is fragmented and aspirated, allowing easy and secure ligation or diathermy, depending on size. This avoids the retraction of oozing blood vessels into the parenchyma, usually associated with blunt finger fracture[8].

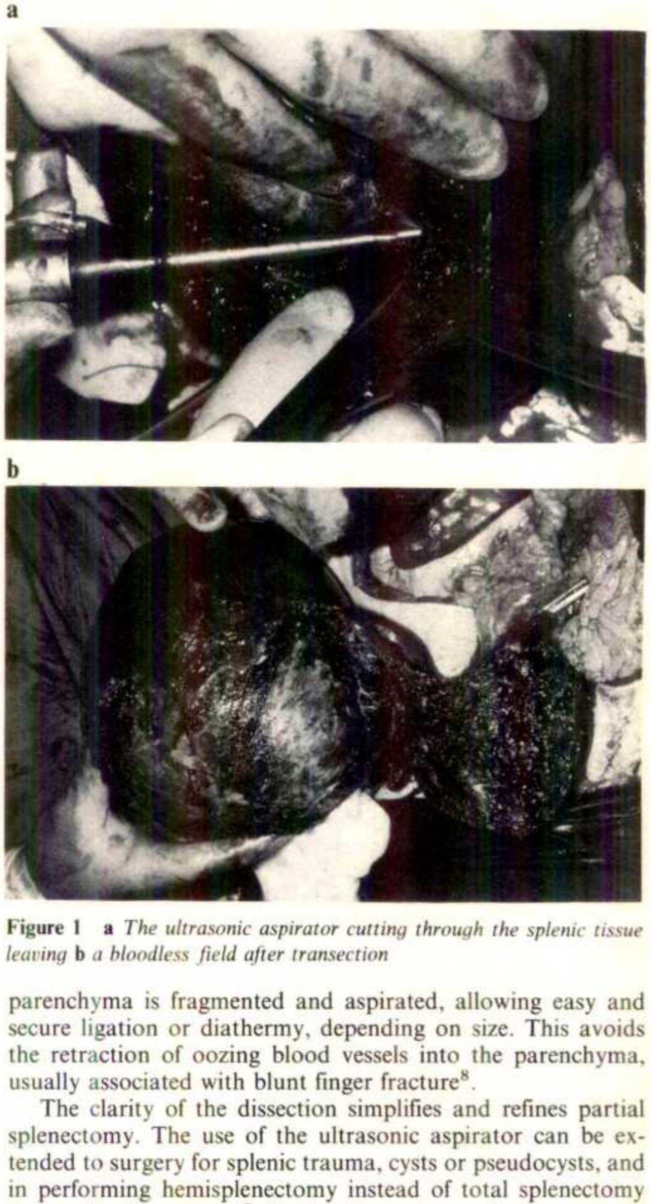

Figure 1 **a** *The ultrasonic aspirator cutting through the splenic tissue leaving* **b** *a bloodless field after transection*

The clarity of the dissection simplifies and refines partial splenectomy. The use of the ultrasonic aspirator can be extended to surgery for splenic trauma, cysts or pseudocysts, and in performing hemisplenectomy instead of total splenectomy for staging laparotomy[9]. In situations where splenic conservation is both logical and desirable, we advocate ultrasonic dissection.

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Treatment of chronic hepatic encephalopathy by the progressive suppression of a spontaneous portacaval shunt via the umbilical vein

H. Bismuth and T. Leese

Hepatobiliary Research Group, Faculty of Medicine, University Paris Sud, France
Correspondence to: Professor H. Bismith, Hepatobiliary Unit, Hôpital Paul Brousse, 94800 Villejuif, France

A patient with posthepatitic liver cirrhosis who developed incapacitating chronic hepatic encephalopathy due to spontaneous portacaval shunting is presented. Progressive suppression of a shunt between the portal and systemic circulation resulted in a successful outcome.

Case report

A 67-year-old woman was admitted in February 1988 with incapacitating chronic hepatic encephalopathy. Posthepatitic cirrhosis had been diagnosed 10 years earlier (antigen HBs negative, antibodies anti-HBs and anti-HBc positive), and for the past year she had experienced increasing encephalopathy resistant to medical treatment. She was no longer able to feed or dress herself and could only walk with help. There was no history of ascites or variceal haemorrhage.

On examination she was overweight (90 kg, 1·65 m), slow mentally, with a marked liver flap making it difficult for her to perform even the simplest of daily tasks. There was no jaundice or ascites. The liver was not palpable, the spleen was enlarged and there was a collateral circulation visible on the anterior abdominal wall.

Investigations revealed that the patient was graded C on the Paul Brousse modification[1] of the original Childs' criteria (albumin 28·9 g/l, total bilirubin 35·4 μmol/l, coagulation factors 35–49 per cent of normal). There were no oesophageal varices at endoscopy. Liver ultrasound revealed hepatic atrophy without any focal defects. The portal vein was patent and measured 19 mm at the hilum, and there was splenomegaly and recanalization of the umbilical vein which measured 20 mm in diameter at the liver hilum. Selective angiography confirmed significant spontaneous portacaval shunting, primarily via the recanalized umbilical vein (*Figure 1*). In view of the severity of the encephalopathy we decided to operate to suppress the umbilical vein. Under general anaesthetic a small transverse incision was made midway between the umbilicus and xiphisternum to the right of the midline. The rectus was split and the peritoneum opened transversely. The round ligament containing the large umbilical vein was exposed and a length of No. 4 silicon tubing, through which had been threaded a reinforcing steel suture, was placed around the entire round ligament without attempting to dissect out the umbilical vein. The two ends of the loop were brought out to the skin surface together via a small incision above the main wound.

On the sixth postoperative day the loop was rotated 180° on the skin surface in a clockwise direction. This manoeuvre was repeated daily, thus gradually constricting the umbilical vein. The progress was followed on plain abdominal X-ray, ultrasound and Doppler examinations. The diameter of the collateral was reduced from 20 mm to 8 mm over a period of 2 weeks with a marked reduction in blood flow and a notable improvement in the patient's encephalopathy. Her mental function improved and she was able to walk and feed herself normally.

She has remained well on follow-up 8 months later with no recurrence of encephalopathy. She has not developed ascites or oesophageal varices. The free ends of the sling have been cut just beneath the level of the skin leaving the constricting loop *in situ* around the umbilical vein.

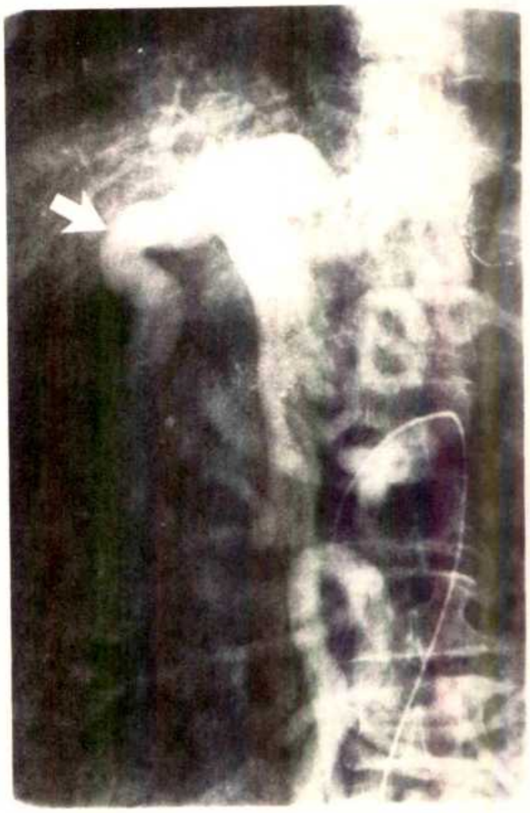

Figure 1 *Venous phase of selective superior mesenteric angiogram demonstrating recanalization of the umbilical vein (arrowed) carrying most of the portal venous blood away from the left portal vein to the systemic circulation*

Discussion

Encephalopathy is a frequent complication of chronic hepatic disease. It is often mild and transient, associated with aggravating factors such as constipation. Severe chronic encephalopathy is usually observed with portacaval shunts, either spontaneous or surgical.

This patient had one principal spontaneous shunt via the reasonably áccessible recanalized umbilical vein. This shunt was suppressed following a relatively minor surgical procedure which was well tolerated despite the patient's major liver dysfunction. The gradual suppression of the shunt enabled the correction of encephalopathy without the development of ascites or oesophageal varices which might have resulted from a sudden increase in portal pressure following complete occlusion of the umbilical vein. It is conceivable that increased portal pressure will result in other spontaneous collaterals opening which may lead to a recurrence of encephalopathy, but after 8 months' follow-up oesophageal varices have not developed and the quality of the patient's life has been transformed by the procedure.

We suggest that in patients with spontaneous hepatic encephalopathy who are not suitable for hepatic transplantation, spontaneous shunts should be identified. In some patients simple surgical suppression of a major shunt may be feasible.

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Short note

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Pernasal catheter perfusion without dissolution agents following endoscopic sphincterotomy for common duct stones

D. F. Martin, J. C. McGregor, M. E. Lambert* and D. E. F. Tweedle*

*Departments of Radiology and *Surgery, Gastroenterology Unit, University Hospital of South Manchester, Nell Lane, Withington, Manchester M20 8LR, UK*

Correspondence to: Dr D. F. Martin

From 80 to 90 per cent of common duct stones can be cleared successfully after endoscopic sphincterotomy[1,2]. This overall figure includes those stones passing spontaneously from the bile duct following the procedure, in addition to those extracted immediately. When stones remain *in situ* after endoscopic sphincterotomy, there is an increased risk of complications[3], particularly cholangitis[4], and consequently a pernasal catheter may be inserted above the stones to ensure drainage and allow cholangiography[5]. The pernasal catheter may also be used to perfuse the bile ducts with dissolution agents such as mono-octanoin[6] and, more recently, methyl-tertiary-butyl-ether (MTBE)[7]. As a controlled study of dissolution treatment via a pernasal catheter after endoscopic sphincterotomy has not been performed, the studies to date are open to the criticism that stones may have passed simply as a result of flushing or drainage rather than dissolution[8]. The current study was performed to determine the effectiveness of perfusion alone.

Patients and methods

Between January 1981 and December 1985, 315 patients with common duct stones underwent a successful and adequate endoscopic sphincterotomy, tailored to the size of the stones. In all patients attempts were made to extract the stones, using an extraction basket and/or a balloon catheter. In 74 patients extraction of all stones was not possible. Failure occurred most commonly when stones, usually in dilated bile ducts, could not be engaged in the basket, or because the balloon catheter slipped around the stones. A 7 Fr wire-guided pigtail catheter (Wilson Cook Medical Incorporated, Letchworth, UK) was positioned above the stones in the bile duct. The catheter was perfused with 2–3 litres of 5 per cent dextrose daily for 3–4 days, at which time cholangiography was performed. When stones were demonstrated, perfusion was continued for a further 4–7 days, after which further cholangiography was performed. If stones were demonstrated, endoscopic retrograde cholangiopancreatography (ERCP) was repeated with attempts at extraction. All patients received a single dose of either mezlocillin 2 g or piperacillin 2 g intravenously before ERCP but antibiotics were not given routinely during perfusion unless clinically indicated. Cholangiography was performed using 30 per cent contrast (Urografin 150®, Schering Health Care, Burgess Hill, UK). Stone size was measured from radiographs with correction for magnification.

Results

There were 32 men and 42 women with a mean age of 74 years (range 40–94 years). Forty-four patients (59 per cent) presented with obstructive jaundice, 14 (19 per cent) with cholangitis, four (5 per cent) with acute pancreatitis, eight (11 per cent) with biliary colic and four (5 per cent) with postoperative retained stones. There were six complications of endoscopic sphincterotomy but no deaths. Pernasal catheterization was successful in 73 of 74 patients. In one patient the catheter could not be positioned above the stones. Fluoroscopy was performed to check that all catheters remained in a satisfactory position after removal of the endoscope and rerouting of the catheter through the nose. Despite securing all catheters firmly, 16 became dislodged before cholangiography could be performed. Two catheters became blocked, both patients developing acute cholangitis which was treated conservatively. No other complications of pernasal catheterization occurred (*Figure 1*).

Of 55 patients in whom perfusion was completed for up to 11 days, 18 had their ducts cleared of stones: ten after 4 days, a further six after 5–7 days and another two after 11 days. In 37 patients the bile ducts were not cleared of stones. The success or failure of perfusion is compared with the size and number of stones in *Table 1*. As might be expected, single stones and small stones were cleared more readily than multiple and large stones. Of the 55 patients in whom the procedure was unsuccessful (tube dislodged or blocked and failed clearance) 40 had their stones removed subsequently at ERCP, 12 underwent surgery and three died more than 1 month after endoscopic sphincterotomy of unrelated causes before bile duct clearance could be ascertained.

Discussion

This study demonstrates that clearance of unextractable stones after endoscopic sphincterotomy can be achieved by pernasal perfusion with a non-dissolving solution in 33 per cent of all patients in whom the catheter remains *in situ*. Clearance during perfusion is related to the size and number of stones in the common duct. In patients with single small stones 88 per cent clearance was achieved compared with 50 per cent clearance of

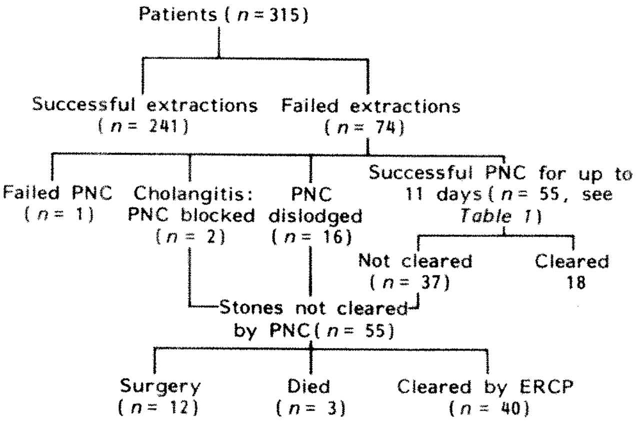
Patients (n = 315)
Successful extractions (n = 241)
Failed extractions (n = 74)
Failed PNC (n = 1)
Cholangitis: PNC blocked (n = 2)
PNC dislodged (n = 16)
Successful PNC for up to 11 days (n = 55, see Table 1)
Not cleared (n = 37)
Cleared 18
Stones not cleared by PNC (n = 55)
Surgery (n = 12)
Died (n = 3)
Cleared by ERCP (n = 40)

Figure 1 *Flow chart indicating the management of 74 patients with failed extraction of stones after endoscopic sphincterotomy. PNC, pernasal catheter; ERCP, endoscopic retrograde cholangiopancreatography*

Table 1 *Numbers of patients with success or failure of duct clearance related to size and number of stones*

Stone size (cm)	Single		Multiple		Total	
	Success	Failure	Success	Failure	Success	Failure
<0·5	7	1	1	2	8	3
0·5–1·0	6	6	2	6	8	12
>1·0	2	15	0	7	2	22
Total	15	22	3	15	18	37

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single stones between 0·5 and 1 cm and 12 per cent clearance of single stones bigger than 1 cm. With multiple small stones 33 per cent of ducts were cleared while with multiple medium-sized stones 25 per cent were cleared. There was no success among patients with multiple stones greater than 1 cm. Others[5,6] have reported that pernasal catheters were well tolerated. However, this was not our experience and may relate to the physical characteristics of the fairly rigid polyethylene catheter used in this study which seems to cause nasal and pharyngeal irritation and, we suspect, is frequently dislodged by patients seeking relief from discomfort. Other complications of pernasal catheterization did not occur unless the tube became blocked.

The efficacy of simple perfusion in clearing the common duct after endoscopic sphincterotomy has not previously been reported in a large series, although Cotton *et al.*[5] reported clearance in eight of 17 patients after perfusion following an initial 48-h period of drainage alone, during which time nine of 26 patients cleared stones from the ducts. However, no mention was made of the efficacy of perfusion related to the size and number of stones. The value of dissolution therapy via a pernasal catheter in patients with unextractable stones after sphincterotomy has been reported[6–10]. However, no controlled series has been performed and indeed some authors[8] feel that this would be unethical. In these published series, successful passage of stones has not always been related to the size or number of stones, making assessment of the efficacy of dissolution compared with mechanical flushing difficult. It seems sensible to propose that where single small stones are left in the common duct after endoscopic sphincterotomy, a period of pernasal perfusion without dissolution agents is likely to be successful. However, with multiple larger stones, dissolution therapy, particularly with MTBE, may be preferable. Where access to extracorporeal shockwave lithotripsy is possible, this may offer a potentially less toxic alternative[11,12].

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Congenital tracheo-oesophageal fistula in an adult

S. J. Peat, T. Paes, E. R. Howard and P. I. E. Jones

Departments of Anaesthesia and Surgery, King's College Hospital, Denmark Hill, London SE5 9RS, UK
Correspondence to: Dr S. J. Peat

The incidence of tracheo-oesophageal fistula is approximately 1 in 4500 live births. Double fistulae, between the trachea and upper and lower segments of the oesophagus, occur in less than 0·3 per cent[1]. This report describes the management of an adult patient with an undiagnosed proximal fistula who suffered repeated pulmonary complications following aspiration of gastric contents during anaesthesia.

Case report

A 26-year-old Caucasian presented for elective caesarean section and requested general anaesthesia. She had undergone tracheo-oesophageal fistula and atresia repair as a neonate, but was in good health. Physical examination revealed the scars of a right thoracotomy and previous caesarean sections Routine preoperative medication included ranitidine 150 mg and magnesium trisilicate mixture 20 ml orally During rapid-sequence induction of anaesthesia there were no signs of regurgitation After delivery, an orogastric tube was passed, 15 ml of fluid were aspirated and magnesium trisilicate mixture 20 ml was given via the tube, which was then removed Soon afterwards, respiration became noisy and a quantity of fluid, contaminated with medication, was obtained on tracheal suction. On completion of surgery, neuromuscular blockade was reversed and the patient was extubated awake in the left lateral position. Cyanosis and wheezing developed progressively, despite prompt treatment with bronchodilators, physiotherapy and oxygen. Chest radiography revealed patchy shadowing at the left base, and blood gas analysis confirmed the presence of severe hypoxia despite an inspired oxygen concentration of 100 per cent (P_{a,O_2}, 6·5 kPa, P_{a,CO_2}, 3·9 kPa). After 24 h intensive care and continuation of bronchodilator and antibiotic therapy, the hypoxaemia resolved.

Subsequently, the patient admitted to mild dysphagia with attacks of coughing and wheezing at night since childhood, which were worse if she slept with fewer than three pillows and during pregnancy. Review of the medical records showed that oesophageal atresia, confirmed by contrast radiography, had been diagnosed shortly after her birth. Right thoracotomy confirmed oesophageal atresia with distal tracheo-oesophageal fistula and primary reconstruction was performed Postoperatively cyanotic attacks delayed her discharge home, but contrast studies failed to demonstrate a fistula or anastomotic stricture. In her 19th year, a barium swallow investigation showed only a 'web' at the repair site and retrograde oesophageal peristalsis. More recently, there was clinical, microbiological and radiographic evidence of pneumonia following all three previous caesarean sections (one under epidural and two under general anaesthesia) On one of these occasions the lower lobes of both lungs were involved and on the other two occasions only the left lung was involved. Heavy growths of *Streptococcus pneumoniae* and *Haemophilus influenzae* had been isolated from the sputum following her first two caesarean sections. After this latest caesarean section, tracheo-oesophageal communication was suspected and further investigations were carried out

At bronchoscopy a posterior opening, 18 cm from the incisors and well above the original repair, was seen in the trachea. The bronchoscope could be passed through this into the oesophagus. Contrast studies later demonstrated this fistula, but only with cinefluoroscopy and the patient prone. At subsequent operation, a catheter was passed bronchoscopically through the fistula into the oesophagus Through a right transverse supraclavicular incision, the strap muscles were divided and the lower pole of the thyroid retracted superiorly, allowing location and division of the fistula Both oesophageal and tracheal defects were then closed and the patient made a successful recovery.

Discussion

The presentation of an overlooked second proximal tracheo-oesophageal fistula in an adult has not been recorded previously. The clinical features are similar to those described in adults with persistent H-type fistula or a recurrence. Furthermore, most patients with corrected oesophageal atresia and/or tracheo-oesophageal fistula suffer oesophageal malfunction, ranging from minor disorders of motility to severe dysphagia and reflux with recurrent pneumonia[2].

Accurate diagnosis depends on contrast studies and endoscopy. In the presence of the H-type fistulae (5 per cent of all cases of tracheo-oesophageal fistula), contractions of the muscle wall of the fistula[3], the oblique caudal direction of the fistula from the trachea and rapid oesophageal transit may protect the airway from reflux of gastric contents, and may hinder fistula recognition during barium swallow examinations, which should be performed with the patient prone[4]. Bronchoscopy, which is superior to oesophagoscopy in the diagnosis of tracheo-oesophageal fistula, locates the fistula and allows the passage of a catheter through it for operative identification. Since upper pouch and H-type fistulae usually occur above the level of the third thoracic vertebra, surgery can be performed through a supraclavicular incision

The diagnosis of tracheo-oesophageal fistula is sometimes difficult on clinical grounds, and it should be considered after unexplained pulmonary aspiration under anaesthesia, the effects of which might have been ameliorated in this case if non-particulate sodium citrate, rather than magnesium trisilicate mixture, had been used for gastric preparation[5]

Acknowledgements

We would like to thank Mr D Gibb, consultant in obstetrics and gynaecology, for permission to report this case, Dr W. Gardener (Department of Thoracic Medicine) and the staff of the Department of Radiology for their help in the management of this patient

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Intervention for graft stenoses: experience following 206 femorodistal reconstructions

J. Thompson, M. McShane, V Gizzard, J. Webster and A. Chant, *Department of Vascular Surgery, Royal South Hampshire Hospital, Southampton, UK*

Femorodistal graft stenoses occur frequently and may progress rapidly to cause graft failure. To assess the incidence of stenoses, 206 patients were studied (74 per cent male, 12 per cent diabetics, mean age 67 years). Ankle brachial systolic indices (ABSI) and Duplex ultrasound were performed 1 month after reconstruction and at 3-monthly intervals thereafter Duplex identified 22 stenoses in 175 grafts which completed serial analyses (105 *in situ* vein, 126 below-knee popliteal or crural anastomoses).

All stenoses were confirmed by angiography. Only five were symptomatic Excluding three early technical lesions, the mean onset was 8 months after reconstruction

Indications for intervention were a fall in ABSI of >0·2, or a haemodynamically high-grade stenosis on Duplex. Treatment was by formal revision or percutaneous transluminal angioplasty (PTA) An initial success rate of 100 per cent was confirmed by angiography and Duplex.

Five of six proximal anastomotic stenoses revised surgically remain satisfactory with a minimum of 1 year follow-up One graft with single vessel run-off occluded at 16 months.

Revisions with PTA performed as follows:

	Proximal $(n=3)$	Intragraft $(n=6)$	Distal $(n=7)$
Recurred (6 months)	3	5	7
Satisfactory (18 months)	0	1	0

Progression of subclinical graft stenoses may be as important as native vessel disease in the aetiology of graft failure. Duplex enables stenoses to be located precisely, so that appropriate treatment can be planned, these data suggest that long-term results of surgical revision are superior to angioplasty

Anticoagulant treatment following vein bypass surgery for femoropopliteocrural arteriosclerosis: influence on patient survival by decreasing the incidence of cardiac deaths

G Kretschmer, E. Wenzl, F. Piza, M. Schemper and E. Gruber, *1st Surgical University Clinic, Alserstrasse 4, A-1090 Vienna, Austria*

The prescribing of anticoagulants for coronary heart disease has been questioned. It seemed promising to test whether anticoagulants might be able to prolong the life of patients suffering from advanced peripheral arterial disease at the femoropopliteocrural level, in which autologous vein bypass surgery was indicated, as cardiac death threatens the life of 50 per cent of these patients The survival status of all patients $(n=1039)$ who had electively received an autologous vein graft during 1970–87 was analysed and Kaplan–Meier estimates were obtained. Ischaemic myocardiopathy alone or in combination with rhythm disturbances played a significant role in decreasing patient survival (median (±standard error of the median) 76·3±4·1 months, no cardiac pathology, 48·8±3·2 months, with cardiac pathology; $P<0{\cdot}0001$ Breslow, $P<0{\cdot}0001$ Mantel). Postoperative anticoagulant treatment influenced the probability of survival in a statistically significant way (median (±standard error of the median) 50·0±2·7 months, no treatment; 117·0±35·5 months, with anticoagulants; $P<0{\cdot}0001$ Breslow, $P<0{\cdot}0001$ Mantel) in particular in the subgroup of patients with cardiac pathology (median (±standard error of the median) 79·3±22·5 months, with anticoagulants; 43·6±3·7 months, without anticoagulants, $P<0{\cdot}0001$ Breslow, $P<0{\cdot}0001$ Mantel). To examine this further, 119 patients who had received a femoropopliteal vein graft at the beginning of 1979 were recruited for a controlled clinical trial and randomly assigned to start phenprocoumon therapy in the second postoperative week (60 patients), or no treatment (59 patients). The median duration of survival for all patients was >60 months, ten patients died in the medicated group and 20 in the control group The treated group had a greater probability of survival ($P<0{\cdot}023$ Breslow, $P<0{\cdot}043$ Mantel) Again, anticoagulants have demonstrated the observed effect by reducing cardiac deaths in the subgroup of patients with cardiac pathology ($P<0{\cdot}018$ Breslow, $P<0{\cdot}028$ Mantel).

Femoropopliteal versus intracrural bypass grafting for limb salvage in patients with an 'isolated' popliteal segment

P.M. Lamont and S.G. Darke (for the Joint Vascular Research Group, UK), *Royal Victoria Hospital, Bournemouth, UK*

Renewed interest in the *in situ* technique has facilitated vein bypass to the distal calf vessels. A degree of doubt exists as to the best site for the distal anastomosis when a patent popliteal artery is 'isolated' from healthy calf vessels by an occluded or significantly diseased intervening segment This multicentre, randomized, prospective trial examines this dilemma.

Fifty-nine patients with critical ischaemia were randomized into two groups· group A, femoropopliteal graft $(n=34)$, group B, femorodistal graft $(n=25)$. All patients had superficial femoral artery occlusions with a patent segment of popliteal artery suitable for grafting seen on arteriography. This popliteal segment had a poor run-off, with either occlusion or stenosis separating it from healthy distal calf vessel(s).

Where possible, *in situ* long saphenous vein was used for bypass, although eight patients in group A and two patients in group B had prosthetic grafts inserted

	Group A	Group B
Primary graft patency	29/34 (85%)	20/25 (80%)
Mean postoperative rise in ankle·brachial pressure index (±s.d.)	0·45±0·29	0·37±0·27
Late graft occlusion (1-year follow-up)	2	3
1-year graft patency in survivors	23/29 (79%)	16/23 (70%)
Limb salvage rate	30/34 (88%)	21/25 (84%)

There were no significant differences in limb salvage or 1-year graft patency rates between the femoropopliteal and femorodistal bypass groups Technical difficulties were encountered more often in the distal group (24 per cent) than in the proximal group (8 per cent). Femorodistal bypass grafting confers no apparent benefit over femoral bypass grafting into a patent popliteal segment, even though the popliteal run-off is impaired or occluded

Influence of smoking and plasma factors on vein graft patency

S.A. Wiseman, G. Kenchington, R. Dain and J.T. Powell (for the Femoropopliteal Bypass Trial Participants)

Interactions between blood-borne factors and arterial grafts may influence patency. Blood samples were obtained 6 months after femoropopliteal vein grafting in 157 patients entered into a multicentre femoropopliteal bypass trial. Cholesterol, lipoproteins HDL, LDL and

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VLDL, apolipoproteins (a), A1 and B, fibrinogen, the fibrin degradation product D-dimer and the smoking markers carboxyhaemoglobin and thiocyanate were measured The 44 patients with grafts that failed within 12 months were compared with 113 patients whose grafts remained patent for at least 1 year

Carboxyhaemoglobin >2·0 per cent with plasma thiocyanate >70 µmol/litre indicated that 41 patients (26 per cent) were untruthful when they said that they had stopped smoking. Based on smoking markers, graft patency in smokers ($n=72$) was 69 per cent at 1 year by life table compared with 85 per cent in 76 non-smokers ($P<0{\cdot}05$). Surprisingly, increased LDL-cholesterol was associated with improved patency at 91 per cent when LDL-cholesterol was above the median, compared with only 66 per cent in the lower half of the range ($P<0{\cdot}01$) Patients with occluded grafts also had significantly higher mean levels of apolipoproteins (a) and A1. Plasma fibrinogen above the median was associated with a 1-year patency of 66 per cent compared with 89 per cent in patients in the lower half of the range ($P<0{\cdot}001$) On multivariate discriminant function analysis the combination of only two variables, plasma fibrinogen and the smoking marker thiocyanate, correctly predicted subsequent patency or occlusion in 129 of the 157 patients

Smoking markers were more sensitive to the risk of graft failure than the history of smoking, which was often inaccurate Fibrinogen and, surprisingly, low levels of LDL-cholesterol with raised apoprotein A1 were associated with graft failure A more forceful approach to stopping patients from smoking, and perhaps therapy to lower plasma fibrinogen levels, appears justified

Low-dose intra-arterial streptokinase in the management of 202 acutely ischaemic legs

D.R Allen, I.B. Faris, L J Ferguson, J.H. Miller, J. Lloyd and A. Robertson, *The Royal Adelaide Hospital, Adelaide 5000, Australia*

Two hundred and two acutely ischaemic limbs in 192 patients (mean age 69·7 years) have been treated with intra-arterial streptokinase. All patients had angiography on admission. a diagnosis of thrombosis was made in 54 limbs (27 per cent), embolus in 37 limbs (18 per cent) and graft occlusion in 111 limbs (55 per cent) An arterial catheter was inserted after angiography and streptokinase was infused as an initial loading dose followed by a maintenance dose Angiograms were performed every 12 h The streptokinase infusion continued until lysis was complete or until the distal vessels had been cleared Limb salvage was achieved in 165 legs (82 per cent) and 37 legs (18 per cent) were amputated Twenty-nine patients (15 per cent) died in hospital, 21 with salvaged legs and eight after amputation Ninety-two of the salvaged legs (56 per cent) required surgery revision after the streptokinase infusion; 67 had graft occlusions with graft revision after clearing the distal run-off vessels and 18 had thrombosed popliteal aneurysms, which were ligated and bypassed after lysing distal clot Seven were distal emboli that had failed to lyse and required formal embolectomy.

Eight embolic occlusions, eight thrombotic occlusions and 16 graft occlusions had incomplete or no lysis after streptokinase and required amputation Minor bleeding complications occurred in 35 limbs and three arteries were perforated Two patients died from cerebral haemorrhage

We conclude that low-dose intra-arterial streptokinase is both safe and useful in the management of acutely ischaemic limbs and that it may be used to convert a difficult surgical option into an easier procedure by clearing distal vessels before surgery.

Epidemiology of atherosclerotic peripheral arterial disease in a random sample of the general population: Edinburgh Artery Study

F.G.R. Fowkes, E. Housley†, C V Ruckley†, C.C A. Macintyre* and R J Prescott, *Department of Community Medicine and *Medical Statistics Unit, University of Edinburgh, and †Peripheral Vascular Clinic, Royal Infirmary of Edinburgh, Edinburgh, UK*

The Edinburgh Artery Study is the first large-scale epidemiological project examining symptomatic and asymptomatic peripheral arterial disease in a sample of the general population in the UK The aims are to examine. (a) aetiological risk factors, and (b) risks of future cardiac and cerebrovascular events The study consists of. (1) a cross-sectional survey of peripheral arterial disease and cardiovascular risk factors and (2) a cohort study of all subjects The purpose of this paper is to describe the methods and some preliminary results of the cross-sectional survey

An age-stratified, sex-specific sample of subjects aged 55–74 years was drawn from the age–sex registers of ten general practices scattered throughout the city of Edinburgh Of these subjects, 1500 attended a clinic for a comprehensive medical examination Peripheral arterial disease was assessed by completion of the World Health Organization (WHO) questionnaire on intermittent claudication, measurement of ankle brachial systolic pressure ratios using a random zero sphygmomanometer and Doppler probe and a reactive hyperaemic test Information was obtained on the following risk factors age, sex, social class, smoking, dietary history, alcohol intake, blood pressure, personality, glucose intolerance, blood lipids, and various haemostatic and rheological factors

Preliminary results indicate that the prevalence of peripheral arterial disease may be slightly higher than detected in other countries Three per cent had intermittent claudication according to WHO criteria, and 14·4 per cent had an ankle brachial systolic ratio <0·9. Further results will describe the distribution of disease in the population and association with other indicators of cardiovascular disease.

Role of exercise testing in minimizing morbidity and mortality in elective abdominal aortic aneurysm (AAA) surgery

K.T. Moran, B Woods, E R Jewell (and G. Shanik), *Lahey Clinic, Burlington, MA 01805, USA*

The role of exercise tolerance testing (ETT) and aggressive haemodynamic monitoring in minimizing morbidity and mortality in 88 consecutive patients undergoing elective repair of AAA was studied Age was in the range 57–84 years (mean 68·2 years) Ninety per cent of patients had two or more and 40 per cent had three or more of the risk factors: hypertension, cigarette smoking, myocardial infarction, angina, congestive cardiac failure or ventricular arrhythmias. Five patients had previously had coronary artery bypass grafts (CABG) Seventy-five patients had ETT and selected patients had thallium tests. All patients were monitored perioperatively with Swan–Ganz and arterial lines

Fifty-eight patients (77 per cent) achieved ≥75 per cent of predicted maximum heart rate (PMHR) on ETT. Thirteen patients had positive ETT, two of whom had angiography and coronary artery bypass grafting before AAA resection Of the 17 patients (23 per cent) who failed to achieve ≥75 per cent PMHR, six had positive thallium tests On the basis of clinical cardiac status or stress test, 20 per cent of all patients were treated with intravenous nitroglycerine perioperatively There were no deaths Mean hospital stay was 8 days Cardiac complications occurred in four patients (5 per cent) with one myocardial infarction, four ventricular tachycardias All four patients had significant coronary artery disease identified preoperatively.

In this study, ETT with selective thallium testing identified patients with severe occult coronary disease requiring CABG before AAA resection, predicted those patients at high risk of cardiac complications and indicated those patients requiring intravenous nitroglycerine perioperatively

Elevated plasma lipoperoxides in atherosclerosis

M D. Stringer and V.V. Kakkar, *King's College Hospital, London SE5, UK*

Many patients with peripheral vascular disease (PVD) and ischaemic heart disease (IHD) do not show the commonly accepted major risk factors and the mechanism of atherogenesis in these individuals is unknown Considerable *in vitro* evidence now exists to support the role of peroxidized lipids in the pathogenesis of atherosclerosis

We have determined plasma lipid peroxide levels in 100 patients with angiographically documented occlusive arterial disease (50 patients with PVD and 50 with IHD) and in 75 control subjects with no clinical features of atherosclerosis. Lipid peroxide levels, measured by a fluorometric assay, were significantly higher in both patients with PVD (mean 4·55 µmol/litre, s.d. 1·23 µmol/litre) and IHD (mean 4·66 µmol/litre, s.d. 1·27 µmol/litre) compared with controls (mean 3·50 µmol/litre, s d. 1·19 µmol/litre, $P<0{\cdot}0001$) There was no significant correlation within any group between plasma lipoperoxides and either total triglyceride or cholesterol values. Furthermore, hypertension, obesity, diabetes, smoking, positive family history and β-blocker/thiazide diuretic intake were not associated with significant differences in lipoperoxide levels

This study provides the first controlled clinical evidence to support a role for peroxidized lipids in atherosclerois

Laser angioplasty with a pulsed neodymium-YAG laser: initial follow-up of the first 40 procedures

J.A. Michaels, F.W. Cross, P. Shaw, M. Raphael, T.J. Bowker, S.G. Bown, M. Adiseshiah and A. Marston, *University College and Middlesex Medical School and Bloomsbury Vascular Unit, London, UK*

Since December 1986, 40 laser angioplasty procedures have been performed using the energy from a pulsed Nd-YAG laser (Lumonics, UK), delivering near infra-red light (1064 nm) in 100 μs pulses of c. 300 mJ per pulse, directly through a transparent sapphire-tipped device All patients had total occlusions of the superficial femoral arteries and symptoms severe enough to warrant surgery, with ulceration or gangrene in eight, rest pain in 14 and severe claudication interfering with lifestyle in the others. The device was introduced through an antegrade puncture of the superficial or common femoral artery and laser recanalization was followed by attempted balloon angioplasty in all cases Occlusions were a mean length of 16 cm (range 2–35 cm); ten patients had previously undergone failed attempts at conventional balloon angioplasty and four had occluded femoropopliteal grafts. Thirty-seven legs of 34 patients were treated, with successful recanalization in 27 and immediate re-occlusion in seven. An average of 60 J was required (range 10–235 J) The 20 successful recanalizations have been followed up for up to 21 months (mean 8 months) with only one late occlusion at 5 months Failed recanalization was due mainly to poor transmission by the delivery device in the early part of the series (five cases), repeated passage of the device down a collateral branch (four cases), or dissection at the site of previous surgery (two cases) Immediate re-occlusion was due to very poor run-off in patients with severely ischaemic limbs (three cases) or technical difficulties with balloon dilatation (two cases) There were no obvious causes in two cases. Complete symptomatic relief was obtained in all the cases of radiologically successful laser angioplasty Early surgery was required in one case following re-occlusion of the artery when an angioplasty balloon failed to deflate, and one patient suffered a skin reaction thought to be due to inadequate removal of the sterilizing solution, which has since been altered. Laser angioplasty can reduce the number of patients requiring bypass surgery and improvements in device and access methods may reduce the number of untreatable cases

Identification of patients with impaired cerebral perfusion reserve before carotid endarteriectomy

A.R. Naylor, C.V. Ruckley, I. Gillespie, R. Cull, P. Sandercock, C.P. Warlow and M.V. Merrick, *The Royal Infirmary and Western General Hospitals, Edinburgh, UK*

Using positron emission tomography, it has been demonstrated that the most accurate predictor of cerebral perfusion reserve (CPR) is the ratio of blood flow to blood volume, which is the reciprocal of cortical transit time[1].

Previous attempts to apply transit times derived from first-pass data have been limited by a failure to correct for dispersion of the bolus following intravenous injection of a non-diffusible tracer Using a new technique, based on the recognition that transit times are additive[2] and which employs a calculation of the γ variate to determine transit times through the aortic arch and brain, this error is corrected and regional median cortical transit times (MCTTs) are determined. This method has been employed in the serial evaluation of 34 patients undergoing carotid endarteriectomy and identified 15 patients in whom there was significant asymmetry of preoperative MCTTs, suggesting impaired CPR.

Restoration of symmetry was evident in eight of the 15 following surgery, with asymmetry persisting in seven The latter included three patients with contralateral internal carotid occlusion, three who developed postoperative neurological deficits and one patient in whom the asymmetry corresponded to an area of old cortical infarction.

Our preliminary data suggest that this simple method may identify those patients with impaired CPR before carotid endarteriectomy and that those patients with computed tomographic evidence of infarction and impaired CPR ipsilateral to the side of operation may be at higher risk of perioperative stroke

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Laser-assisted percutaneous transluminal angioplasty (LPTA): results and complications

E.R.T.C. Owen, S.A. Moussa, R.A. Wilkins and J.D. Lewis, *Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex, UK*

The enabling event in percutaneous angioplasty is the ability to cross the lesion with a guide-wire. Laser probes under fluoroscopic control have recently been introduced to assist in crossing occluded arterial segments.

Over a 15-month period, 125 patients underwent conventional angioplasty, 22 patients (mean age 72 years, range 50–91 years) have undergone 24 laser-assisted percutaneous transluminal angioplasties All lesions treated were total occlusions distal to the common femoral artery and varied in length from 2 to 40 cm. Laser (Trimodyne 1 5 mm 'hot-tip', Trimodyne Incorporated, Tustin, California, USA) was only used when the occlusion could not be crossed by conventional guide-wire technique. Of the 24 occlusions, eight (33 per cent) could not be crossed with laser; two of the 16 lesions crossed could not be dilated because of vessel perforation Thus, 14 (58 per cent) lesions were dilated; one re-occluded immediately but 13 remained patent, all patients showing signs of revascularization, and improvement in ankle.brachial pressure index in ten. Seven of these re-occluded within 2 months three early (within 24 h) and four late (2 days, 1 and 3 weeks, 2 months) In only six patients the dilated vessel remained patent for up to 1 year.

Complications occurred in 14 (58 per cent of procedures), perforation (8 per cent) and extravasation (36 per cent) are attributable to laser None adversely affected the outcome in the limb except by preventing angioplasty. Laser-assisted percutaneous transluminal angioplasty in its present format has only found a limited place in management The longer distal occlusion remains a problem for the interventionist, as does the long-term maintenance of patency after successful laser-assisted percutaneous transluminal angioplasty

Percutaneous angioscopy of peripheral arteries

A. Gehani, S. Ashley, S.G. Brooks, A.B. Latif, R.C. Kester and M.R. Res, *Cardio-Thoracic Research Unit, Killingbeck, Leeds, UK*

Angioscopy provides a new perspective of peripheral vascular disease. We have used high resolution, ultrathin, flexible fibre-optic angioscopes (1 4 mm and 1 8 mm outer diameter) for percutaneous assessment of seven iliac or femoral arterial occlusions in six patients before and after angioplasty. Procedures were carried out with either a fast rotating tip atherectomy device (Kensey catheter), or sapphire tip modified Nd-YAG laser energy and, in one case, balloon angioplasty alone A clear view was obtained by displacing flowing blood with a high-flow saline flush A microchip camera attached to the eyepiece of the scope provided continuous video monitoring and recording of each procedure

Angioscopic views were compared with pre-, intra-, and post-procedure angiograms Angioscopy identified the pathological nature of stenoses and occlusions (thrombotic or atheromatous) precisely. In addition, angioscopy was more sensitive at detecting the presence of non-stenotic pathology. Angioscopy provides a useful assessment of the initial results of angioplasty. In particular, angioscopy detected intimal flaps and dissections more readily than angiography and, on the basis of this information, additional therapeutic manoeuvres were employed, such as 'laser welding' of obstructive intimal flaps Angioscopy detected fresh thrombus in two out of seven arterial sheaths, despite adequate heparinization.

We conclude that angioscopy complements angiography in the assessment of occlusive peripheral arterial disease, and provides additional information which is particularly useful for guidance and valuation of new percutaneous recanalization techniques

Homologous vein in secondary access surgery

J.J.F. Steijling, R.W.H. Van Reedt Dortland, A. Dimitroff and T. Theodorides, *State University Hospital Utrecht, Utrecht, The Netherlands*

Since 1983, homologous vein grafts have been used in secondary access surgery in the Department of Vascular and Transplantation Surgery of the State University Hospital, Utrecht. One hundred and seventy-six arteriovenous fistulae were constructed with homologous vein in 149 patients with end-stage renal disease The cumulative patency is 73 per cent after 53 months (life-table method).

In 64 grafts (36·4 per cent) 137 reinterventions were necessary because of thrombosis (83), stenosis (30), aneurysmal dilatation (18) and infection (six). No signs of rejection were seen on histological investigation. There was no serious morbidity or mortality related to the fistulae.

Patients, nurses and medical staff prefer these fistulae over other material in secondary access because of easy puncture, low incidence of complications and easy management of any complications.

Computerized storage of angiograms

E. Antebi, J. M. Lehmann and M. Borstein, *Hasharon Hospital, Petach Tikva, Israel*

A computerized system for the storage and enhancement of X-rays has been developed in association with a major electronics firm in Israel. The system consists of an IBM–PC compatible computer, a video-television camera, an optical disk and a television screen. The X-ray pictures are stored on hard disk or diskettes, together with additional information about the patient. The computer can process the pictures to improve contrast and edge enhancement and to enlarge selected parts of the picture, features especially applicable to angiograms. Further improvements are anticipated in the direction of transmission to satellite computers. Access to pictures is easy and fast, and prompt comparison of X-rays is made possible.

Management of unilateral iliac occlusion

S.D. Parvin and P.R.F. Bell, *Department of Surgery, University of Leicester, UK*

Unilateral iliac occlusion may be treated surgically by aortobifemoral, axillofemoral, iliofemoral or femorofemoral bypass. The results of 69 unilateral iliofemoral bypasses performed over a 7-year period have been reviewed. Indications included claudication (21), critical ischaemia (39), previously infected graft (7) and trauma (two). Risk factors included hypertension (20), previous myocardial infarction (eight), angina (11), cerebrovascular accident (nine), diabetes mellitus (ten), cigarette smoking (41) or past history of cigarette smoking (20). The mean age of the group was 61 years (range 16–84 years).

Grafts originated from the common iliac artery (59), from the aorta (seven) or from previous Dacron® (E. I. du Pont de Nemours and Company, UK) grafts (three). They were inserted into the femoral artery (common/profunda/superficial) in 55 cases, into the above-knee popliteal in nine and into the below-knee popliteal artery in five. Thirteen femoropopliteal bypasses, two femorofemoral bypasses and one profundoplasty were performed at the same time.

The 30-day mortality rate was 2 of 69 (3 per cent). At 12 and 24 months cumulative patency was 94 per cent and 86 per cent respectively ($n=45$ and $n=29$). Neither indication for operation nor the patency of the superficial femoral artery influenced outcome. Iliofemoral bypass is as safe and effective as transperitoneal aortofemoral bypass (97 per cent patent at 1 year) and femorofemoral bypass (91 per cent patency at 1 year), and better than axillofemoral bypass. There is no risk of steal from the donor limb as in femorofemoral bypass and no increased mortality or risk of impotence as in transperitoneal aortofemoral bypass. Iliofemoral bypass may be the treatment of choice for unilateral iliac occlusion.

Primary and secondary vascular reconstruction by femorofemoral bypass

S.H. Silverman, P.B. Brown, M.H. Simms, R. Downing, F. Ashton and G. Slaney, *Queen Elizabeth Hospital, Birmingham, UK*

Reconstruction of unilateral iliac artery occlusion can be achieved by many techniques, of which femorofemoral bypass (FFB) is one which has various reported long-term results. We undertook a retrospective review of 102 patients who underwent FFB and analysed the results by life-table methods in two groups. Group 1 ($n=69$) were those in whom no previous surgery for inflow to the leg had been performed. Group 2 ($n=33$) were those having FFB as a secondary reconstruction, a prior procedure having failed. Five-year postoperative cumulative graft patency, limb salvage and patient survival were 80, 78 and 51 per cent, respectively, in group 1, and 41, 52 and 66 per cent, respectively, in group 2. By comparison, in 400 patients undergoing orthotopic aortofemoral reconstruction in our unit during the same time-period the 5-year cumulative graft patency was 79 per cent.

The variation in reported long-term results of FFB arises as some reports are concerned with primary reconstruction only while others cover primary and secondary procedures. The results of FFB for primary reconstructions are comparable to those of orthotopic bypass grafts and therefore support the use of FFB in all patients presenting with strictly unilateral iliac artery occlusion.

Popliteal aneurysms presenting as acute limb ischaemia

M.W. Kissin, R. Pullan, D.J.A. Scott, M. Horrocks and R.N. Baird, *Bristol Royal Infirmary, Bristol BS2 8HW, UK*

Popliteal aneurysms (PAs) should have surgical bypass to a patent tibioperoneal segment before spontaneous thrombosis or embolization eliminates the critical outflow bed. This orthodox approach clearly covers asymptomatic patients who are low risk and who have PAs which are greater than an undefined minimum critical size. What approach should be used when the initial presentation is progressive limb ischaemia and how should an acutely thrombosed aneurysm be investigated?

The outcome of 22 PAs in 19 male patients from 1978 to 1988 was assessed. Streptokinase infusion was employed to clear thrombus in four patients and arteriography and pulse generated run-off (PGR) was used to image and assess adequacy of the outflow tract. Bypass operation was chosen for nine fit patients with large, asymptomatic PA and for ten patients with ischaemia in whom there was adequate run-off.

Symptoms	No. of patients	Outcome		
		Normal	Claudication	Amputation
Asymptomatic	9	9	0	0
Chronic ischaemia	3	2	1	0
Acute ischaemia	7	3	0	4

The results show an increased likelihood of a poor outcome when the leg was acutely ischaemic ($P<0·01$) and when foot pulses were absent ($P<0·01$). Outcome was unaffected by the absence of a popliteal pulse, the presence of a contralateral PA, the material used for bypass or the operative approach.

The combined use of early arteriography with streptokinase infusion and assessment by PGR may give the best chance of selecting patients for successful bypass.

A warning from 12 years of popliteal aneurysm treatment

L. Hands, J. Collin and P.J. Morris, *Nuffield Department of Surgery, John Radcliffe Hospital, Oxford OX3 9DU, UK*

In the 12 years 1975–87, 35 popliteal aneurysms in 26 patients were managed by a specialist vascular surgical service. The treatment outcome has been assessed at recent follow-up of these patients. Twelve aneurysms were symptomless and 23 were causing local discomfort, were thrombosed, ruptured or associated with distal embolization. Twenty-one aneurysms were treated operatively with ligation and bypass grafting and 14 were managed conservatively. Equal proportions of symptomless and symptomatic aneurysms were treated surgically. All five of the symptomless popliteal aneurysms managed conservatively were still symptomless 4–8 years (median 6·5 years) later whereas only four of the seven symptomless aneurysms treated operatively were symptomless 1–2 years (median 2 years) later. Ten (71 per cent) of the legs with symptomatic popliteal aneurysms treated operatively were symptom-free 6 months–9 years (median 6 years) later, compared with only three (33 per cent) of the symptomatic aneurysms managed conservatively, 1–6 years later (median 1 year) $\chi^2=4·97$; $P<0·05$. A deep venous thrombosis occurred in six (29 per cent) limbs after operation on a popliteal aneurysm. We conclude that operative treatment of popliteal aneurysms should be reserved for those which are symptomatic. A symptomless limb can only be made worse by arterial surgery.

Prevalence of significant peripheral vascular disease in the diabetic population

A. Gee, G.C. Moir, S.W.J. Smith and S.G. Darke, *Royal Victoria Hospital, Bournemouth, UK*

An acute thrombotic or infective episode in the limb of a diabetic patient with pre-existing peripheral vascular disease may lead to major amputation Theoretically, this might be avoided by prospective reconstruction if this was undertaken in anticipation of such an event. To estimate the proportion of patients at risk a systematic evaluation by clinical examination and Doppler ankle systolic pressure measurements was undertaken in 162 known diabetics cared for within one general practice catering for 13 500 patients. An ankle:brachial systolic pressure ratio $<0·6$ was arbitrarily taken as an indicator of 'significant' peripheral vascular disease

This was found in one or both limbs of 26 of the patients examined (16 per cent). Only nine of these patients, however, had symptoms of claudication, rest pain or ischaemic tissue necrosis. The mean age of this group was 77 years (range 50–87 years) compared with 55 years in those with ratios >0 6. Of those affected, nine were insulin dependent, 14 were on oral hypoglycaemic agents and three were on diet alone. The low ankle pressures correlated well with the absence of pedal pulses on clinical examination

Sixteen of these patients were referred to a vascular clinic where the distribution of the peripheral vascular disease was determined on clinical grounds. In seven it was thought to be principally infrapopliteal, in five there was evidence of femoropopliteal occlusion, and in four there was aortoiliac stenosis together with an uncertain degree of more distal disease. Where appropriate angiography has been undertaken The possible clinical relevance of these findings is discussed

A prospective study of atherosclerotic renovascular disease causing renal failure: incidence and treatment outcome

G. Hamilton, J.E. Scoble, E.R Maher, R. Dick and J.F. Moorhead, *Royal Free Hospital, London, UK*

Renal artery stenosis from atherosclerosis is a potentially curable cause of renal failure. To date, studies have looked only at selected groups of patients with relatively good renal function referred for angioplasty or surgery This prospective study (at a nephrology centre serving a population of c. 1 million) was carried out over an 18-month period to identify patients with renal failure (creatinine clearance $\leqslant 30\,\mathrm{ml/min^1}$) in whom renovascular disease might be the cause.

Out of 64 patients of all ages, recruited for renal replacement therapy, ten were confirmed by digital subtraction angiography as having renovascular disease as the cause of their renal impairment All ten were >50 years of age, with a mean age of 65·2 years and a serum creatinine of 453 μmol/litre Bilateral disease was present in eight and one had a single functioning kidney Five patients had significant ischaemic heart disease, six had cerebrovascular disease and five had peripheral vascular disease.

Four patients were treated by angioplasty, with significant improvement in one Two patients underwent surgical revascularization, with improvement sufficient to discontinue dialysis in one. Of the remaining four patients, one declined surgery, one had an infarct during angiography and one suffered severe refractory congestive cardiac failure.

This study confirms that atherosclerotic renovascular disease is a common cause of renal failure in patients aged >50 years (29 per cent) In this series, all the patients presented with advanced renal failure and significant improvement in glomerular filtration rate was achieved in only two Although potentially curable, concomitant coronary and cerebrovascular disease makes these patients very high-risk candidates for intervention

Severe finger ischaemia in professional cricketers

D. Wilkinson and R.C. Kester, *St. James's University Hospital, Leeds, UK*

Occupational vibration exposure is a well recognized cause of digital ischaemia but this has not been described in cricketers. Two fast bowlers have recently suffered a rapid onset of rest pain and ulceration in the index finger of their bowling arm. Digital Doppler pulses were absent, rewarming after a cold-stress test was markedly delayed and arteriography confirmed digital arterial occlusion in the symptomatic finger and the adjacent middle finger. The remaining fingers were normal Both were treated with ten daily 8-h intravenous infusions of iloprost, a stable prostacyclin analogue, at a maximum dose of $2\,\mathrm{ng\,kg^{-1}\,min^{-1}}$ In each case the symptoms improved rapidly, and both players resumed bowling.

Two batsmen of a similar age were examined; both regularly field in the slips. Although asymptomatic, both had several absent digital Doppler pulses and rewarming after cold-stress test was markedly delayed in all the fingers of both hands.

The digital involvement may reflect the pattern of occupational trauma, throwing the ball, catching the ball or jarring transmitted through the handle of the bat. The use of iloprost to treat severe occupational hand ischaemia warrants further investigation

Silent myocardial ischaemia in patients with peripheral vascular disease

E.L. Rose, A. Lahiri, E.B. Raftery and J.D. Lewis, *Northwick Park Hospital and Clinical Research Centre, Harrow, UK*

Previous work has shown that only 8 per cent of preoperative patients with peripheral vascular disease (PVD) have no demonstrable coronary artery disease (CAD) on coronary angiography. A significant amount of this CAD is clinically silent with only c 50 per cent having a history of angina.

We assessed 15 preoperative and postoperative vascular patients for evidence of myocardial ischaemia. Eight patients had abdominal aneurysms, five had aortoiliac disease, one had femoral and one had carotid disease. None of the patients had severe cardiac symptoms or would have normally undergone cardiac investigations, seven had a history of angina, of whom three had a previous myocardial infarct.

Reversible myocardial ischaemia, as detected by thallium scintigraphy, was detected in 13 patients but was not predicted by a reduced left ventricular ejection fraction (EF) on radionuclide angiography.

		Thallium scintigraphy reversible defects	
		Present ($n=13$)	Absent ($n=2$)
Angina	Present ($n=7$)	7	0
	Absent ($n=8$)	6	2
Radionuclide angiography	EF $<50\%$ ($n=5$)	5	0
	EF $>50\%$ ($n=10$)	8	2

Of those with positive thallium scans, to date: ten have had coronary angiography confirming severe coronary disease; five have gone on to coronary artery bypass grafting, with one waiting; and one has had coronary artery angioplasty

These data demonstrate the high prevalence of silent myocardial ischaemia in patients with PVD. Over 50 per cent of perioperative deaths are due to CAD; if they are to be reduced, all patients with CAD should be identified and treated accordingly before operation is considered The absence of a history of angina does not exclude reversible myocardial ischaemia

Ultrasound scan screening for abdominal aortic aneurysm

C.S. Loh, I.M. Stevenson, A.V.O. Wu and B. Eyes, *Walton Hospital, Rice Lane, Liverpool L9 1AE, UK*

A group of 1293 men >55 years old were invited to take part in an ultrasound scan screening programme for abdominal aortic aneurysms (AAAs). Six hundred and fifty-seven men attended for scanning (50 8 per cent) Their age ranged from 55 to 94 years (mean $=63$ years 11 months) The abdominal aorta was not visualized in 19 individuals because of excessive bowel gas and in one because of gross abdominal lymphadenopathy Maximum abdominal aortic diameter ranged from 11 to 52 mm (mean $=20$ 1 mm). AAAs (maximum diameter >30 mm) were found in 19 individuals (2·9 per cent) The prevalence of AAAs in this study was 1·3 per cent in the group <65 years old and 6 5 per cent in the group >65 years old. Follow-up scan had so far shown progression in the size of the AAA in one individual. One patient had undergone successful surgical resection and grafting and two other patients had since died. Ultrasound scan screening for AAAs is practicable but should be directed to the population aged >65 years to improve cost effectiveness. Follow-up scan of small AAAs will provide further knowledge regarding the natural history of this condition.

Results of ultrasound follow-up of 102 abdominal aortic aneurysms

R.A.P. Scott, H.A. Ashton, D.N. Kay and R.C. Bowyer, *St. Richard's Hospital, Spitalfield Lane, Chichester, West Sussex, UK*

The study has now identified 102 patients with an aorta $\geqslant 3$ cm out of 2056 patients screened Sixty-nine of the 102 have had repeat scans and 25 have shown an increase in diameter on repeat scan. Twenty have been invited to come to outpatient clinics after their third scan to explain the findings and the reasons for further scans. Ten have reached the criteria for considering surgery (i.e. an aortic diameter ≥6 cm, an increase in diameter of >1 cm per year or the onset of symptoms) and seven have undergone surgery, all with a good outcome. Three were assessed and found to be unfit for planned surgery and continue to be observed. Conversely, 95 with aortic dilatation ≥3 cm have not undergone surgery. None of the patients screened has died of ruptured abdominal aortic aneurysms, although nine have died of other causes.

As a result of this study it seems likely that it is possible to identify: (a) a high-risk group that may require surgery (25 that increased in size on repeat ultrasound scan and those ≥6 cm), (b) a low-risk group (77 who did not increase in size and 1954 who had an aorta <3 cm) who should not require surgery.

Abdominal aortic aneurysms (AAAs): a familial disease

J. Collin and J. Walton, *Nuffield Department of Surgery, John Radcliffe Hospital, Oxford OX3 9DU, UK*

One hundred patients (97 men) undergoing surgery for AAA were interrogated about their first-degree relatives.

One father and four mothers were still alive and one patient had never known his parents. Of 295 siblings, 132 were known to be dead (77 men). Sixty-eight surviving siblings were not available for study and 29 were excluded because they were either >80 years old, or were men <50 years or women <55 years old. Sixty-six siblings were invited for ultrasound examination of the aorta and 27 (41 per cent) attended.

No female relative was known or discovered to have an AAA. Of 132 men who died aged >50 years, three (2·3 per cent) were thought to have died from a ruptured AAA. One of the 57 surviving brothers aged >50 years, who was not examined, was already known to have an AAA. Four AAAs were discovered in 17 men who attended for ultrasound examination and three of these (diameter 4·7–8·5 cm) have since been resected.

Hearsay evidence from AAA patients suggested that the prevalence of AAA in 207 male first-degree relatives who lived beyond 50 years was 1·9 per cent. Ultrasound examination of one in 12 of these relatives revealed an additional unsuspected prevalence of 23·5 per cent. These findings provide strong support for the view that AAA is a familial disease.

Aneurysm surgery in octogenarians

I.C. Currie, D.J.A. Scott, P. Vowden, R. Phillip, K.R. Poskitt, R.N. Baird and M. Horrocks, *Bristol Royal Infirmary, Bristol BS2 8HW, UK*

To justify surgery in the octogenarian there must be a low perioperative mortality and a reasonable postoperative mortality.

We have studied 33 octogenarians undergoing aortic aneurysm repair (14 elective, 19 emergency) between 1980 and 1988 at the Bristol Royal Infirmary. Survivors were given a structured interview at home (I.C.C.) to assess quality of life, which was compared with that of age and sex matched controls.

	Elective	Emergency	Total
Number of patients	14	19	33
Operative mortality	1 (7%)	7 (37%)	8
Late mortality	3 (21%)	8 (42%)	11
Survivors	11	11	22
Mean survival	677 days	818 days	
Range	4–72 months	7–67 months	

In the elective group there was a low operative mortality and a good postoperative quality of life. In the emergency group mortality was not different from younger patients operated on during the same period, and of the ten emergency patients interviewed eight reported having a good quality of life.

Twelve postoperative aneurysm patients were compared with 12 similar control subjects taken from an age and sex matched general-practice population. The incidence of angina, breathlessness, previous stroke, impaired mobility, performance of daily activities, emotional problems and support did not differ between patients and controls.

Aortic surgery, both elective and emergency, cannot be denied to octogenarians on the basis of age alone. These elderly arteriopaths can obtain good direct surgical benefit while remaining independent.

Fibrinolytic enhancement versus surgical ablation of superficial incompetence in the prevention of venous ulcer recurrence: a controlled clinical trial

K.G. Burnand, M.C. Stacey, G.T. Layer, K. Lloyd, F. deBeaux and N.L. Browse, *Department of Surgery, St. Thomas' Hospital, London, UK*

Stanozolol, an anabolic steroid known to enhance fibrinolysis, has been shown to reduce perivascular fibrin deposition and to improve lipodermatosclerosis (pigmentation and induration) in limbs with severe venous disease[1]. It is not known if this improvement in the skin reduces the risk of future ulceration.

Sixty-nine patients have been enrolled in a randomized trial to compare surgery and elastic stockings with stanozolol and elastic stockings in the prevention of ulcer recurrence. Surgically treated patients had all sites of superficial valvular incompetence eradicated. Foot volumetry and phlebography were carried out in all limbs to confirm the presence of venous disease, and other causes of ulceration were carefully excluded. Patients in both groups were well matched for the number of previous ulcers, the longest period of unhealed ulceration and evidence of a previous deep vein thrombosis, all of which appear to influence the likelihood of breakdown.

Eight patients out of 38 treated by stanozolol, and six patients out of 31 patients treated by surgery, have developed new ulcers within 4 years of entry. There is no statistical difference between the number of ulcer recurrences in the two randomized treatment groups, $P = 0{\cdot}1$. Ten of the 20 patients who refused to enter the study and who were treated by stockings alone have already developed new ulcers.

Stanozolol and stockings appear to be as efficacious as surgery and stockings in preventing the recurrence of venous ulceration.

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A new approach to chronic venous ulcers in the community

C. Moffatt, D.D.I. Wright, D. Besley, C.N. McCollum and R.M. Greenhalgh, *Department of Surgery, Charing Cross Hospital, London, UK*

At least 150 000 patients suffer venous ulcers in the UK, many failing to heal for months or years, costing £2500 per ulcer per patient per year. A four-layer bandage (4LB) technique provides sustained graduated compression with 40 mmHg at the ankle, which heals most ulcers by 12 weeks, but few patients benefit while treatment is confined to hospital practice.

A 12-week trial clinic linked to a vascular unit was established at a local group practice, all staff were trained in the 4LB technique and volunteers were recruited to help transport patients.

In a population of 7500, 21 (0·28 per cent) patients with leg ulcers were identified, with a mean age of 78 (range 52–91) years and average ulcer duration of 21 months. Venous and arterial disease were assessed by Doppler and three patients with ankle pressure indices <0·8 were unsuitable for the 4LB. The remaining 18 patients attended or were brought by volunteers to the community clinic at the general practitioner's surgery. After 12 weeks, all but two ulcers were completely healed, with a mean time to healing of 3·9 weeks, and patients were then fitted with class 2 compression stockings (DuoMed®, Medi UK Ltd., Hereford, UK). In the 4 months after the trial the remaining two ulcers have healed and there have as yet been no recurrences.

This pilot study demonstrates that multilayer compression bandaging is applicable in the community. The majority of chronic leg ulcers can be healed and the potential savings in resources are considerable.

Fibrin clearance and calf pump function

H. Gajraj and N.L. Browse, *St. Thomas' Hospital, London SE1, UK*

The tissue and blood fibrinolytic activity of patients with venous leg ulceration is reduced. Fibrin cuffs are found around the capillaries of affected skin and these are thought to block the diffusion of oxygen. It is unclear whether this reduction in fibrinolysis is generalized and whether it is related to calf pump function.

Radioactively labelled (^{125}I) fibrin microclots were formed subcutaneously in the arms and legs of 33 subjects with healed venous ulcers, ten subjects with bilateral varicose veins and 11 healthy controls by the injection of 0·05 ml fibrinogen and thrombin. The clearance half-life was calculated for each site. The calf pump function of all subjects was assessed by foot volumetry, measuring the relative expelled volume (EV_{rel}) after 20 knee-bends and the half-volume refilling time ($TV_{\frac{1}{2}}$) at rest.

	Fibrin clot half-life in hours (mean ±s.d.)	
	Arms	Legs
Controls	16·9±5·3	18·1±5·3
Subjects with varicose veins	16·7±2·3*	24·7±6·5†
Subjects with healed ulcers	17·2±3·5*	
Non-ulcerated		25·1±8·9‡
Ulcerated		36·9±21·1§

Compared with control, Mann–Whitney *U* test. *not significant; †$P<0·05$; ‡$P<0·01$; §$P<0·001$

A significant negative correlation was found between the fibrin-clot clearance half-life and $TV_{\frac{1}{2}}$ ($r_s=-0·27$, $P<0·01$). The correlation between the fibrin half-life and EV_{rel} was not statistically significant.

Fibrin clearance is prolonged from the legs only and is related to the degree of calf pump dysfunction

Early clinical results after implantation of a small-bore elastomeric prosthesis

W.F. Tait and D. Charlesworth, *University Hospital of South Manchester, Manchester, UK*

For patients who have pre-gangrene of a leg, no saphenous vein, and in whom a femorodistal bypass has failed there is little alternative to amputation.

We have used a new 4 mm diameter elastomeric prosthesis as a bypass in 24 such limbs In seven, a bypass (polytetrafluoroethylene) had failed and in seven a femoropopliteal bypass with vein had failed In the remainder the vein was either unsuitable or had been removed for a coronary artery bypass graft

Eight bypasses occluded early, and all were characterized by (a) femorotibial bypass, (b) single vessel run-off; (c) ankle:arm ratio unmeasureable One infected but patent graft was removed Fifteen bypasses have remained patent, the longest for 13 months (mean 7 months) The mean (±s.d.) ankle:arm ratio was 0·3±0·1 before operation and 0·76±0·2 after operation. Six of the 15 femorodistal bypasses were done in conjunction with a proximal (iliac) reconstruction.

Preliminary results suggest that a 4 mm elastomeric graft can work in circumstances where currently available prostheses may not

Chronic lower-limb venous insufficiency: an approach to management

P.E. Kiely, *Bon Secours Hospital, Cork, Ireland*

Using a live display of lower-limb venous manometry, the initial part of this programme illustrates normal venous haemodynamics at rest and during exercise This contrasted with the abnormal ambulatory venous pressure response in a limb with venous insufficiency (VI) By way of graphics and manometry the normal muscle pump mechanism is demonstrated. The different ways by which the muscle pump is compromised are shown VI is defined and its pathological consequences are discussed A classification of limbs with venous insufficiency is proposed simple varicose veins, complicated varicose veins; mixed venous insufficiency, post-phlebitic limb

The second part of this programme illustrates the approach to management Since the scope of surgery is limited to the removal of incompetent superficial veins the initial surgical endeavour is directed towards accurate anatomical diagnosis of all superficial incompetences so that surgical ablation will be complete In clinical examination particular emphasis is placed on the importance of pattern in the display of varicose veins as a guide to the incompetent systems and to the identification of perforating veins. Use of the Doppler probe as an essential adjunct to clinical diagnosis is demonstrated The operative techniques of ligation and stripping are shown briefly

Lastly, the importance of functional evaluation of limbs with deep venous insufficiency is demonstrated with particular emphasis on the value of tourniquet walking pressure in identifying those limbs with significant superficial incompetences In this way superficial and deep venous function are differentiated so that no limbs are denied the benefit of surgery to the superficial veins, nor are any subjected to unnecessary operation.

The programme is based on experience in the surgical management of >3000 limbs

Leucocyte trapping in the peripheral circulation in response to changes in venous pressure

H.J. Scott, P.D. Coleridge Smith and J.H. Scurr, *Middlesex Hospital, London, UK*

Leucocytes become trapped in lipodermatosclerotic skin in patients with chronic venous insufficiency (CVI). Is this effect produced by a rise in venous pressure associated with CVI?

Patients with normal deep veins ($n=10$) and CVI ($n=10$) were studied using direct venous sampling from the dorsal foot and hand veins, and dynamic capillary video microscopy of ankle skin Subjects rested supine for 30 min, then sat with the lower limbs dependent for 60 min to raise the venous pressure, and finally lay supine for a further 30 min. In another ten patients, blood was taken from a dorsal hand vein and cephalic vein of the forearm, initially with the arm supine, then dependent for 15 min and finally with a cuff applied to the upper arm at 80 mmHg for 15 min. The results were as follows

Examination	Group	Supine 30 min	Dependent 60 min	Supine 30 min	*P*
Capillill loops per square nanogram at ankle	CVI	10·4(2·0–29)*	8·3(2·0–17)*	12·3(1·0–22)	*0·021
Leucocyte loss (%)	Foot CVI	2·8(−12–17)*	−0·3(−22–13)*	−6·2(−4·9–7)	*n s
Arm measurements		Supine	Dependent (15 min)	Cuff (80 mmHg)	*P*
Leucocyte loss (%)	Fore-arm	0*(ref value)	−1·1(−8·0–1·8)	12(2·7–20)*	*0·006
	Hand	0*(ref value)	−4·9(−10–0·1)	11(−11–31)*	*0·044

All values are given as median and range in parentheses Significance by Wilcoxon paired test

Raising the venous pressure in the arm to 80 mmHg caused white cell trapping in both the hand and forearm. Leucocyte trapping in the feet did not occur although the reduction in functional capillary loops confirms that microvascular changes have occurred in CVI legs The venous pressure rise in response to dependency was too small to influence white cell trapping in the feet.

Randomized study of carotid endarteriectomy versus saphenous vein bypass in the treatment of extracranial cerebrovascular disease

M.C. Crowson, M.X. Gannon, T.I.M. Gardecki and J.D Hamer, *Queen Elizabeth Hospital, Birmingham, UK*

Endarteriectomy has generally been abandoned in vascular reconstructive procedures in favour of autogenous vein or prosthetic bypass grafts. However, endarteriectomy remains the commonest vascular procedure for internal carotid stenosis. Reported restenosis and occlusion rates vary from 1 to 49 per cent; our own experience demonstrated an 18 per cent occlusion rate We have previously reported a pilot study of 37 consecutive vein bypass grafts

We now report a prospective randomized study comparing vein bypass grafts to endarteriectomy in 76 patients (vein bypass 39, endarteriectomy 37) All patients had a postoperative Doppler ultrasound scan which was repeated at 6 weeks Follow-up was then performed at 3-monthly intervals using clinical assessment and Doppler ultrasound scanning, and at 6-monthly intervals using digital subtraction angiography.

To date, the mean follow-up is 14 months. One patient died postoperatively from a myocardial infarct At 6 weeks follow-up six (16 per cent) of the endarteriectomies were occluded and one (3 per cent) vein graft Further follow-up demonstrated that the overall occlusion and stenosis rate was 24 per cent for endarteriectomy and 10 per cent for vein grafts Neurological events (transient ischaemic attack/cerebrovascular accident) occurred in 14 per cent of the endarterectomy patients and 5 per cent of the vein grafts.

These preliminary data suggest that vein bypass may be a superior procedure for the treatment of symptomatic internal carotid stenosis.

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Penetrating trauma to the carotid vessels: Lebanese war experience

G.S. Khoury and H. Hajj, *American University of Beirut, Lebanon*

Between April 1975 and July 1987, 510 neck injuries were treated at the American University of Beirut Medical Center The carotid vessels were involved in 48 patients, resulting in 53 carotid injuries.

The mean age was 25·3 years; shrapnel injuries were the commonest (46 per cent) followed by bullet injury (33 per cent), 39 patients had a laceration and five had complete disruption Only three presented as acute arteriovenous fistula (AVF) Neurological deficit was present in 13 patients, of whom six were in coma.

Shock was present in 14 patients, of whom five had a neurological deficit Six patients underwent ligation of the injured vessels, three of which were external carotid arteries. Nine patients were not operated on initially, six of them had chronic AVF and three were in coma; the rest underwent surgicl repair.

Nine patients died, giving an overall mortality rate of 19 per cent, four of these patients died due to complications of multisystem failure, giving a 10 per cent mortality rate for isolated carotid injury There was definite improvement in the repaired group, but the haemodynamic status seemed to affect the mortality rate significantly ($P<0.01$) Follow-up of the surviving patients revealed five with persistent neurological deficit in the repaired group (33 patients) and four patients had chronic AVF, only two patients had false aneurysms.

Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland

The Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland will be held on 23–24 November 1989 in Dundee, UK. For information contact, Mr James Forrester, Department of Surgery, Ninewells Hospital, Dundee DD1 9SY, UK

Correspondence

Subtotal colectomy or colonic preservation in the treatment of colonic cancer?

Sir

The paper by Marston (*Br J Surg* 1989; **76**: 71) proposes many arguments in favour of subtotal colectomy with ileorectal anastomosis as the treatment for colonic cancer. He justifies this by claiming that the function of the colon is to absorb water and that loss of the colon results in diarrhoea which can usually, but not always, be controlled by diet and drugs. Whilst the absorption of water and electrolytes has been accepted as the main function of the colon it now seems likely that our knowledge of colonic function is far from complete. Jackson[1] proposed that the human colon, with its normal colonic microflora, might well play a significant part in human nutrition and metabolism. Some of our recent studies have centred on the role of the colon in nitrogen metabolism[2,3]. The human colon is relatively inaccessible and we have taken advantage of the colonoscope to gain access to the lumen of the intact colon. We have inserted labelled urea (^{15}N stable isotope) through the biopsy channel of the colonoscope as a marker of colonic nitrogen metabolism. We have demonstrated that the colon is permeable to urea, that intraluminal hydrolysis occurs and that significant proportions of urea nitrogen can be incorporated into the body pool of nitrogen. The majority of the previous work on colonic function, including colonic nitrogen metabolism studies[4], has been using perfusion techniques following peroral intubation of the caecum. This has entailed preliminary cleansing of the colon followed by perfusion of large volumes (of the order of 10 ml/min) of the solution in question. When one considers that the normal intestinal transit time is 60–72 h and that 40–60 h of this are spent in the colon[5], these perfusion studies may well give misleading results in terms of normal colonic function. The expanding field of research on the metabolism of fibre in the colon[5] and the more recent work on nitrogen metabolism strongly suggest that much further work needs to be done before definitive conclusions can be reached about colonic function. Without this information the prophylactic removal of normal colon has to be a point of considered clinical judgement and it has yet to be proved that it is in the best interests of a patient with colonic cancer.

B. J. Moran
A. A. Jackson
S. J. Karran

Southampton General Hospital
Southampton SO1 6HU
UK

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Severe intra-abdominal sepsis

Sir

I read with interest the paper by Mr Huizinga and colleagues which compares single agent antibiotic therapy with combination therapy in what the authors define as 'severe intra-abdominal sepsis' (*Br J Surg* 1988; **75**: 1134–8). I would like to object to the use of the term 'severe' in the context of their study.

What is the cohort of patients looked at? It included practically every single patient with peritonitis seen over the study period who required laparotomy. The only patients excluded were those allergic to the antibiotic agents and 'those who appeared moribund'. The median age of these patients is only about 30 years. When the origin of the intra-abdominal sepsis was investigated more carefully, it was found that in no less than 78 per cent of cases, the infection originated from gastroduodenal perforations, and traumatic injuries to the small bowel and the appendix. Furthermore, in only 10 per cent of cases was the source of sepsis the colon or the pancreas. None of the patients suffered from postoperative peritonitis. In support of their contention that the abdominal sepsis was 'severe', the authors report the following criteria: delay between diagnosis and treatment, amount of fluids used for resuscitation, tachypnoea, hypoxaemia, acidosis and clouded sensorium which existed in 69 per cent of their patients. The overall mortality rate in these patients was a mere 3 per cent.

Although there is no strict definition of what constitutes severe intra-abdominal sepsis the current trend is to accept as 'severe' sepsis the following: firstly, that which originates owing to factors such as postoperative leaks, the colon and infected pancreatic necrosis (the majority of the patients considered in this trial would fall into the category of relatively less severe peritonitis[1,2]); secondly, most studies of severe peritonitis include a large proportion of patients compromised by old age, intercurrent chronic disease and established organ failure, the mortality of such patients being in the order of 30 per cent[3], which is in sharp contrast with the 3 per cent quoted by the authors. This last figure most certainly suggests an APACHE II score of less than 10 in most of their patients, reflecting the minor physiological insult of the infection on relatively young and previously healthy organ systems[4,5]. Such parameters as hypoxia, tachypnoea or clouded sensorium should have been graded objectively in this prospective trial.

I wish also to point out that when 'all skin wounds were managed by delayed primary closure' it is difficult to understand how wound infections were reported in 11 patients. Is the failure to achieve a delayed primary closure considered a wound infection or is it a secondary infection of the wound left open?

With the kind permission of the authors I wish to suggest the following conclusion to their otherwise excellent trial: adequately treated intra-abdominal generalized sepsis occurring in young patients and originating from perforated peptic ulcers and injuries to the small bowel and from the appendix have a negligible mortality, independent of the antibiotic regimen used.

M. Schein

University of the Witwatersrand
Johannesburg
South Africa

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Surgical aspects of a district hospital combined gastroenterology clinic

Sir

The article by Holmes *et al* on 'Surgical aspects of a district hospital combined gastroenterology clinic' (*Br J Surg* 1988, **75**: 1105–7) was surely meant to be provocative! The fall in operation rate from 35 per cent to 20 per cent is attributed to a reduction in the numbers of certain operations (e.g. operation for peptic ulcer), but there is no mention of the impact of new technology.

In our hospital, diagnostic endoscopy has largely replaced the barium meal: it provides previously unobtainable information about the bile ducts and pancreas, and resolves many problems in the colon. Therapeutic endoscopy is used in the upper gastrointestinal tract (dilatation of benign oesophageal strictures, palliation of gastro-oesophageal cancers, injection sclerotherapy of varices and balloon dilatation of achalasia), in the biliary tract (endoscopic sphincterotomy and extraction of bile duct stones, palliation for malignant strictures and dilatation of benign strictures) and in the colon (endoscopic polypectomy). Most of the patients treated by these methods would formerly have required surgical operations

Therapeutic radiological procedures have also contributed to the reduction in operations (e g treatment of intussusception, percutaneous transhepatic biliary stenting, ultrasound guided biopsy of liver masses and drainage of abscesses and pancreatic pseudocysts)

Anyone considering the formation of a combined gastroenterology clinic in 1989 needs to take account of these technical developments and decide how to distribute this workload between physician, surgeon and radiologist

D. F. A. Watkin
D. P. Fossard
D. L. Carr-Locke

Leicester Royal Infirmary
Leicester LE2 7LX
UK

Diagnosis and management of abdominal pain

Sir

In the recent paper on the use of advisers in the diagnosis and management of patients with abdominal pain (*Br J Surg* 1988, **75** 1173–5), the authors report 711 patients who were admitted with acute abdominal pain. They draw the conclusion that advisers were unnecessary until the patient was admitted. The figures used to support this conclusion are based on just over 50 per cent of the series The exclusions were for a variety of reasons, including the absence of a record of a second opinion or a recorded diagnosis. This might cast some doubt on the conclusions

The reader is left with the impression that the policy of the unit was restricted to a decision whether to admit or not rather than to come to a probable diagnosis which, in turn, would suggest appropriate investigations The sceptic might consider that there were other reasons for admission than the exact requirements of the individual patient

The authors draw attention to the paradox of the inability of the senior house officer to admit a patient without obtaining a second opinion as compared with the power to discharge a patient without such advice. Such a policy is wide open to misuse and leads to inappropriate admission or discharge Unfortunately, there is no list of final diagnoses of the patients who were admitted, let alone those who were discharged. Most of the given references included all patients seen.

The authors state that the majority of patients were admitted, although no percentage is given. What was the majority? It has been shown in the references that it is a common finding that 90 per cent are admitted, but when the system is subject to audit with or without computer diagnosis it is found that the more appropriate figure for admission is around 60 per cent[1] Such a change would free an enormous number of beds. Our own earlier work has confirmed this and after 16 000 patients seen consecutively in our accident and emergency department, all with acute abdominal pain and computer-assisted diagnosis, the figure for admissions remains around 60 per cent[2] It is also clear that the number of re-referrals remains lower than it was before the policy was introduced Similar figures have been reported from many centres in the world

In the light of our experience, we would disagree with the conclusion that the use of the computer-assisted system would be more effective than a second opinion We believe that the computer should not be considered as an alternative to a proper clinical opinion It has been shown by us and many others that the computer is more accurate than the senior house officer who is not using the system However, more importantly, the doctor using the computer system is disciplined to take a more appropriate history and to examine the patient more adequately as the findings are recorded for posterity and peer review The computer issues a challenge, producing better records and thereby better conclusions with regard to management This results in the senior house officer being as good as, if not better than, the computer The results of the combination are fewer admissions, better communication of information to seniors, greater accuracy at the front door, fewer unnecessary laparotomies and more appropriate use of investigations.

Perhaps the strongest case for the use of the computer can be made on the grounds of audit of performance, creation of a patient record and the education of junior staff In our system this has been extended to include collection of investigation results and management decisions Herein lies an important power of modern technology which has led to the creation of management packages[3-5].

A. A. Gunn

Bangour General Hospital
Uphall
West Lothian
UK

1 Gunn AA. The diagnosis of acute abdominal pain with computer analysis *J R Coll Surg Edinb* 1976, **21** 170–2
2 Gunn AA. Twenty five years of audit—a personal experience In: Russel CS, ed *Recent Advances in Surgery*. Edinburgh Churchill Livingstone, 1988. 287–311
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Non-operative management of splenic trauma in adults

Sir

The traditional treatment for splenic trauma has been splenectomy However, the observation that splenectomized children may develop overwhelming post-splenectomy infection has reversed the classical treatment of splenectomy for the management of splenic trauma. Conservative procedures such as splenorrhaphy, partial splenectomy and splenic autotransplantation have become common practice. The success of non-operative management in children with splenic trauma[1] and the observation that most adult patients have spontaneous cessation of bleeding before surgery, together with the ability to assess splenic damage by computerized tomography or ultrasonography induced us to attempt non-operative management in selected cases of adult splenic injury

We adopted a policy of restricting surgical intervention to patients where associated injuries were suspected Our non-operative method allowed blood transfusion to a maximum of 300 ml/h or a total of 3000 ml as long as vital signs were controlled. The patients were observed in the intensive care unit for the first 2 days. Bed rest was instituted for 7 days and vigorous exercise forbidden for 2 months Repeated computerized tomographic assessments were undertaken at 30-day intervals until complete resolution of the splenic damage was seen.

Using this method we have treated 15 consecutive patients with splenic rupture demonstrated clinically and by computerized tomography or ultrasonography. The mean age has been 35 years (8–62 years) with an average requirement for blood transfusion of 2500 ml. In one case operation was performed when an associated injury was suspected In every other case surgery was avoided and complete resolution of the splenic lesion was documented within a 2-month follow-up period.

These preliminary results have encouraged us to continue with this policy of non-operative management for isolated adult splenic trauma

M. Armengol
B. Oller
J. A. Salva

Autonomous University of Barcelona
Barcelona
Spain

1 Buntain WL, Gould HR Splenic trauma in children and techniques of splenic salvage *World J Surg* 1985; **9**: 398–409

Thermal gradients

Sir

We read with interest the recent paper by Rogers *et al* on thermal gradients in the anorectum and their contribution to continence (*Br J Surg* 1988, **75** 1083–5) and were pleased that this independent group should find a 'clear temperature gradient from the rectum to the anal verge'. As they rightly point out this is an essential prerequisite if temperature sensation contributes to sensory discrimination of rectal contents. Bearing in mind the differences in technique, their results are similar to our own previous study[1]

Their conclusion, however, reveals a serious shortfall in their understanding of sensory physiology They state that the difference in temperature between rectal contents and anal canal is below measured thermal thresholds in the anal canal and therefore that temperature sensation can play no part in continence.

Firstly, the sensation of rectal contents is not one of hot or cold but rather the feeling of a semi-solid/liquid (stool) or a gas (flatus). These experiences are 'blended sensations' (like the feeling of wetness on the skin) and are the result of a mixture of mechanical and thermal stimuli[2] Whether or not the temperature component alone needs to reach conscious thresholds is unknown but this is not a condition for temperature to have an influence (subthreshold or suprathreshold) in the perception of a 'blended' sensation

Secondly, even if conscious awareness was necessary, the thermal stimulation of the anal canal depends on factors such as surface area exposed to the stimulus, which can have a profound effect on measured thresholds[3] We used a 1-cm long thermode to study thermal sensitivity. Rogers *et al* stated that the healthy anal canal is 4 cm long[4] and sampling of rectal contents occurs at least as far as the mid-sphincter[1] This would result in 2 cm or more of mucosa being exposed to the stimulus, twice the length of the thermode The area exposed would be further increased by folds and corrugations of the anal mucosa.

Finally, the authors are concerned with the length of anal canal sensitive to thermal stimuli and yet in the few subjects studied they use a different stimulus, namely mucosal electrosensitivity to 'assess the length of sensitive mucosa'. At best this can only be described as illogical but it also assumes a direct correlation between thermal and mucosal electrostimulation which is not the case[5]. Furthermore, the lowermost rectum is also sensitive to thermal stimuli, albeit at higher thresholds than the anal canal[6].

R. Miller
D. C. C. Bartolo
F. Cervero
N. J. McC. Mortensen

University of Bristol
Bristol BS2 8 HW
UK

1. Miller R, Lewis GT, Bartolo DCC, Cervero F, Mortensen NJMcC Sensory discrimination and dynamic activity in the anorectum: evidence using a new ambulatory technique. *Br J Surg* 1988, **75**: 1003–7.
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Author's reply

Sir

We note the comments of Mr Miller *et al* on our paper (*Br J Surg* 1988, **75**. 1083–5) with interest Our paper is experimental evidence to support the original criticism[1] on theoretical grounds of the paper 'Anorectal temperature sensation. comparison of normal and incontinent patients'[2] which drew inappropriate conclusions about the role of temperature sensation in the anal canal and its possible relationship to the continence mechanism.

We were pleased to see that the points made in this original criticism were taken by the authors and incorporated into a subsequent paper[3] The median temperature differences they measured between the rectum and anal canal were between 3 and 4 times lower than the median thresholds necessary for conscious appreciation of temperature[2,4] This confirms our data and supports our conclusion that under normal physiological circumstances 'the conscious appreciation of temperature of faeces passing from the rectum to the anal canal is impossible during the anorectal "sampling reflex" '[5]

Their point about 'blended sensation' needs answering. There is scant evidence that subconscious appreciation of temperature change takes place in the anal canal or anywhere else Indeed the theory that the sensation of wetness includes the presence of mechanical and thermal stimuli is based on archaic observations on the effec of anterolateral chordotomy[6]. A recent review states 'Ordinarily, sensations of wetness include the presence of mechanical and thermal stimuli, but the necessary conditions have not been delineated, and the methods of testing patients have not been detailed appropriately'[7].

We would like to remind Mr Miller *et al* that all their data is related to conscious appreciation of temperature change in the anal canal, which is poor licence for the extrapolation of this data into the realms of 'subconscious' or 'blended sensations'. Acceptable as this may be for the discussion section of an MD or MS thesis we feel it is unacceptable in the presentation of a paper in a scientific journal

Our advice to anyone intending to set out to investigate the role of temperature sensation in the continence mechanism would be to measure and compare the anorectal temperature gradients and the thresholds of temperature sensation in each individual subject

J. Rogers
M. P. Hayward
M. M. Henry
J. J. Misiewicz

Central Middlesex Hospital
London NW10 7NS
UK

1 Rogers J Anorectal temperature sensation *Br J Surg* 1987, **74** 1189
2 Miller R, Bartolo DCC, Cervero F, Martensen NJMcC Anorectal temperature sensation. a comparison of normal and incontinent patients *Br J Surg* 1987; **74** 511–15.
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Book reviews

Current Surgical Diagnosis and Treatment. 8th ed

L. W Way 182 × 260 mm Pp.1223 Illustrated 1988 Hemel Hempstead Prentice Hall £29 95.

The appearance of the eighth edition of this textbook of surgery testifies to its continued success and popularity although not, I suspect, on this side of the Atlantic. It remains in much the same form as previous editions, being the product of 82 authors primarily from the West Coast of America and under single editorship

After a general introduction and chapters relating to general medical and surgical topics important in the management of all patients, and including (perhaps with increasing relevance) 11 pages on 'legal medicine for the surgeon', the remainder of the book covers all organ systems and includes chapters on ENT, ophthalmology, orthopaedics, neurosurgery, cardiac surgery, plastic surgery, urology and paediatric surgery

Since the seventh edition there has been an updating of key references throughout the text (up to 1986) and several chapters have been either extensively rewritten, e.g surgical nutrition and head and neck tumours, or substantially revised

The editor is to be congratulated on achieving a uniform style throughout the text and adhering to the stated aim of 'serving as a ready source of information about diseases managed by surgeons and emphasizing quick recall of major diagnostic features and brief descriptions of disease processes Throughout the text the quality of line drawings is good, particularly where they remain simple The reproduction of radiographs is poor which perhaps explains some notable exclusions, e g not a single endoscopic retrograde cholangiopancreatogram in the chapter on the pancreas There is also considerable variety in illustrations of surgical technique. Based on the diagrams, I would be happy to remove an appendix but not atheroma from the carotid arterial system nor repair an aortic aneurysm.

These criticisms lead to my main concern and that is the perennial question 'to whom is the text directed'? The claim is that the intended audience comprise students, house officers and medical practitioners. As a text for the pre-fellowship trainee it is inadequate in detail in many areas and would, of necessity, have to be read in combination with other texts. The post-fellowship registrar seeking detailed information on a surgical disease or procedure would be disappointed although the up-to-date references might well point him in the correct direction However, I feel that this text can be recommended unreservedly to medical students in that it gives a good and comprehensive account of current surgical practice and is more than adequate for final examination. It remains to be seen whether a soft cover volume of over 1200 pages gains in popularity or, indeed, lasts the course

P. J. Finan

Consultant Surgeon
The General Infirmary at Leeds
Leeds LS1 3EX
UK

Growth Factors and Other Aspects of Wound Healing

A Barbul 156 × 235 mm Pp 329. Illustrated. 1988. New York· A R Liss $68.00.

This book presents the proceedings of the Second International Symposium on Tissue Repair held in Tarpon Springs, Florida in May 1987 I went to the first symposium in 1982, but I missed the second and was pleased therefore to review this book

It is a specialized book of great interest and is highly recommended to those involved in or interested in the biological aspects of wound healing, with particular emphasis on growth factors. All the well-known names in the field (mostly from the USA) are represented here, giving a complete and up-to-date account of recent advances There is a wealth of references after each chapter, albeit a little repetitive. It is a pity that the whole book was not typeset in the style of the introduction. I was not informed of its price, but I doubt whether it should grace the bookshelf of anyone other than the surgeon or biologist working in the field

D. J. Leaper

Department of Surgery
Queen Mary Hospital
Hong Kong

Low Level Laser Therapy: A Practical Introduction

T Ohshiro and R. G Calderhead. 221 × 254 mm. Pp 129. Illustrated. 1988. Chichester. John Wiley & Sons. £30 50

Low level laser therapy (LLLT) is the Cinderella of medical laser applications The majority of laser treatments work by heat coagulation or vaporization of tissue with high energy laser beams; LLLT is said to exert its effect quite differently by mechanisms of biostimulation in tissue healing, nerve regeneration, and other areas which are difficult to assess in clinical practice. It is by no means clear how LLLT works in tissue healing or indeed, some may say, whether it even works at all.

This book represents a summary of LLLT work carried out, mainly in China and Japan, using helium–neon and GaAs lasers in the milliwatt range The physics of the lasers is discussed, followed by a number of examples of clinical applications of LLLT. Most of the work described involves wound healing and pain relief studies, and many of the case reports are well described and convincing in nature, particularly those involving hyperpigmentation of the skin The wound healing work is less convincing and some of the science in these areas is slightly patchy. There are a number of irritating errors, such as that where it is said that photons of different energies travel at different speeds (page 13). On page 55 it is said that human skin absorbs light maximally in the 500–650 nm range whereas absorption is higher at shorter wavelengths It is difficult to keep an open mind on LLLT; most readers of this book will already be convinced either that it works or that it does not, and there is very little in the text to confirm or refute either viewpoint

F. Cross

Senior Registrar
The Middlesex Hospital
London W1
UK

Clinical Progress in Nutritional Research

A Sitges Serra, A. Sitges Creus and S. Schwartz-Riera. 152 × 229 mm. Pp.281. 1988. Basel Karger. £53.20.

At the Ninth Congress of the European Society of Parenteral and Enteral Nutrition in Barcelona last year, 26 individuals from 13 countries were invited to present lectures on selected topics This paperback contains papers from these individuals and is a rather mixed production. Some of the papers consist of reviews and others of precise presentations of new work. The papers vary in length from two to 26 pages. Some are wideranging reviews referring to the knowledge gathered mainly by others and some reviews emphasize the authors' contributions Thus a paper by Singh and Chandra on 'The use of immunological indices for nutritional assessment and outcome' contains 30 references of which the first 15 refer to the authors' work in this field. The topics chosen are important for those undertaking research in this field and the book will also be useful as a reference for others who wish to extend their knowledge in specific areas of nutrition but, as the title implies, this is not a textbook of nutrition for clinicians.

D. E. F. Tweedle

Consultant Surgeon
Withington Hospital
Manchester M20 8LR
UK

Management of Gunshot Wounds

G J. Ordog 178 × 254 mm. Pp.461. Illustrated 1988. Amsterdam. Elsevier. $75 00

This book is unlikely to be widely read by surgeons on this side of the Atlantic where gunshot wounds are still comparatively rare in most clinical practices The multi-author text deals exhaustively with most aspects of gunshot wounds, but there is much overlap and repetition between the chapters. I found two chapters by the editor (ballistics and socioeconomics) particularly worthwhile

Most surgeons and trainees will benefit more from reading a standard trauma text (several have recently been published), that puts gunshot wounds in their true perspective as mechanisms of injury Those venturing to Belfast or the Bronx will find the book of more than passing interest but given the British antipathy for firearms there can be only a limited market for this book here

B. J. Rowlands

Professor of Surgery
Royal Victoria Hospital
Belfast
UK

Notices and announcements

6–9 May 1989
First Annual UCLA Program on Endovascular Surgery
Beverley Hills, California, USA
Information: Rosie Melia, UCLA Extension, Continuing Education in Health Sciences, 10995 LeConte Avenue, Room 614, Los Angeles, California 90024-1340, USA

18 May 1989
Debate: Balloon and Laser Angioplasty will Reduce the Necessity for Vascular Surgery
London, UK
Information· Mr John Wolfe, St. Mary's Hospital, The Queen Elizabeth Queen Mother Wing, Cockburn Lecture Theatre, Praed Street, London W2 1NY, UK

26 May 1989
Annual Meeting of the British Association of Endocrine Surgeons
Lille, France
Information Mr A. W. Goode, Honorary Secretary, British Association of Endocrine Surgeons, The Surgical Unit, The London Hospital, London E1 1BB, UK

25–26 May 1989
International Symposium: Surgery in Europe
Rome, Italy
Information: Professor Sergio Stipa, V Clinica Chirurgica Policlinico Umberto I, Viale del Pliclinico, 00161 Rome, Italy

12–13 June 1989
Cholelithorama: Total Gallstone Management
London, UK
Information: BDI Conferences Ltd., 3 Beaconsfield Terrace Road, London W14 0PP, UK

19–21 June 1989
Tripartite Meeting
Birmingham, UK
Information Mr Roger Grace, The Royal Hospital, Wolverhampton, UK

21–23 June 1989
71st Annual Meeting of The Endocrine Society
Seattle, Washington, USA
Information The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

24–27 June 1989, 28–30 June 1989
Second Mediterranean Surgical Congress
Athens, and continued in Heraklion, Crete, Greece
Information. Ms Peggy Alexopoulou, Public Relations Centre, 56 Hippocratous Street, 106 80 Athens, Greece

6–7 July 1989
70th Meeting of the Surgical Research Society
Newcastle upon Tyne, UK
Information: Mr Alan J Rich, Department of Surgery, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne, UK

13–15 July 1989
XIVth International Update on Liver Disease
London, UK
Information. Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

15–16 July 1989
Hong Kong Surgical Forum
Hong Kong
Information. Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

21–24 August 1989
4th International Symposium on Obesity Surgery
London, UK
Information: Mr E. R T. C. Owen, Academic Surgical Unit, The Queen Elizabeth Queen Mother Wing, St. Mary's Hospital, Praed Street, London W2 1NY, UK

27 August–1 September 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Informtion: International Congress and Convention Association, PO Box 50006, Tel Aviv 61500, Israel

6–8 September 1989
Fourth World Congress of the International Society for Diseases of the Oesophagus
Chicago, Illinois, USA
Information· 4th World Congress of the International Society of Diseases of the Oesophagus, 911 Busse Highway, Park Ridge, Illinois 60068, USA

10–15 September 1989
3rd International Symposium on Inflammatory Bowel Diseases
Jerusalem, Israel
Information: International Congress and Convention Association, P O. Box 5006, Tel Aviv 61500, Israel

10–15 September 1989
XIV World Congress of Otorhinolaryngology Head and Neck Surgery
Madrid, Spain
Information: Technical Exhibit Manager, XIV World Congress of Otorhinolaryngology, C/ Velazquez, 90-5th floor, 28006 Madrid, Spain

11–16 September 1989
33rd World Congress of Surgery
Toronto, Canada
Information. 33rd World Congress of Surgery, Congress Canada, Congress Management, 73 Richmond Street West, Suite 300, Toronto, Canada M5H 1Z4

17–26 September 1989
Frontiers in Gastroenterology: Colorectal Disease
Birmingham, UK
Information· Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

17–20 September 1989
The Centenary Congress of the Polish Surgical Association
Kraków, Poland
Information: Organizing Committee, ul Kopernika 40, 31-501 Kraków, Poland

21–23 September 1989
Annual General Meeting of the Association of Surgeons in Training
Cardiff, Wales, UK
Information. Mr B Taylor, Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

15–21 October 1989
Recent Advances in Pancreaticobiliary Surgery
Edinburgh, UK
Information· Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

15–17 November 1989
Fourth EORTC Symposium on Advances in Gastrointestinal cancer: Research and Treatment
Strasbourg, France
Information: J. P. Arnaud MD CMCO, 19 rue Louis Pasteur, Schiltigheim BP 120, 67042 Strasbourg Cedex, France

17–19 November 1989
Eight Annual Trauma Symposium
El Paso, Texas, USA
Information: William Beaumont Army Medical Center, El Paso, Texas, USA

18–22 November 1989
9th Biennial Asian Congress on Thoracic and Cardiovascular Surgery
Taipei, Taiwan, Republic of China
Information: The Secretariat, The 9th Biennial Asian Congress on Thoracic and Cardiovascular Surgery, P O Box 68-439, Taipei, Taiwan, Republic of China

23–24 November 1989
Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland
Dundee, UK
Information. Mr James Forrester, Department of Surgery, Ninewells Hospital, Dundee DD1 9SY, UK

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information Dr Joseph W C Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

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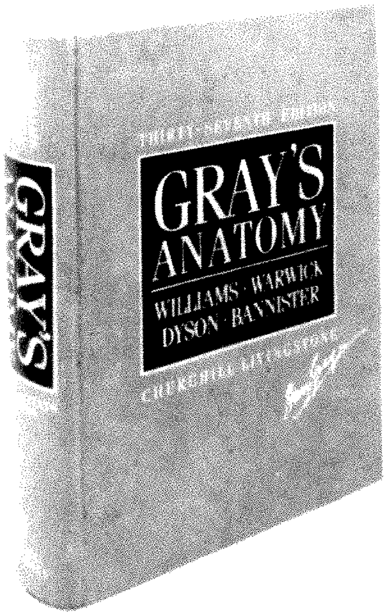

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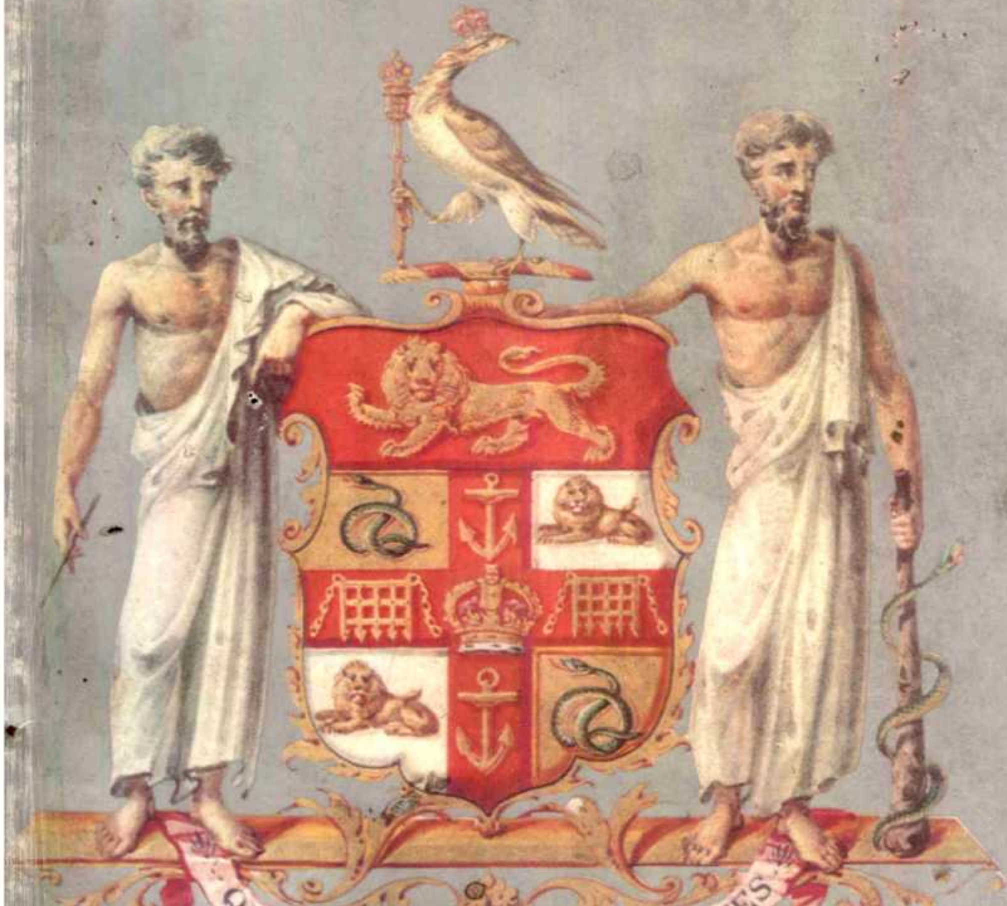

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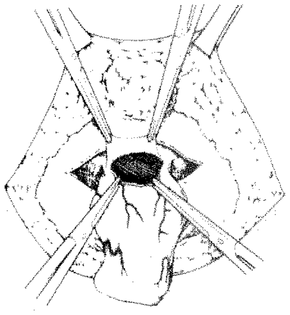

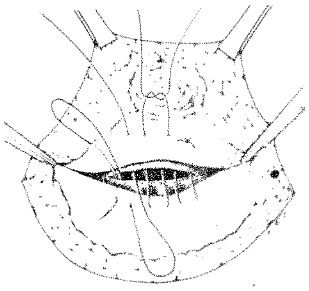

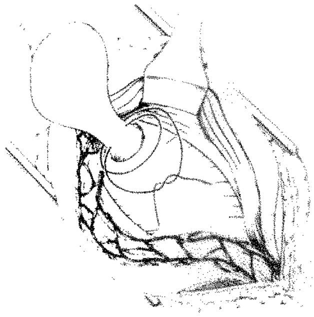

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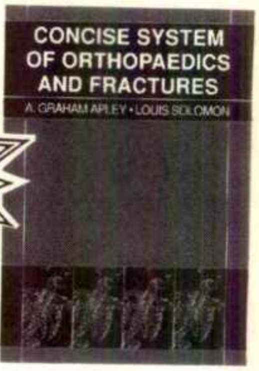

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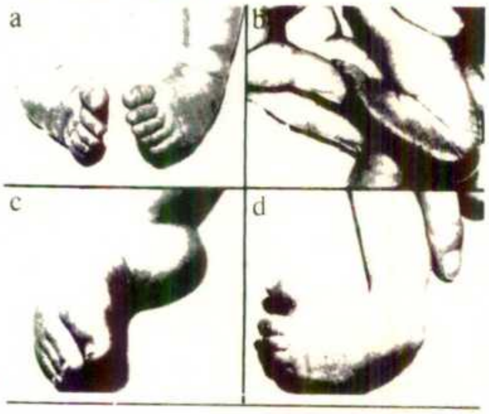

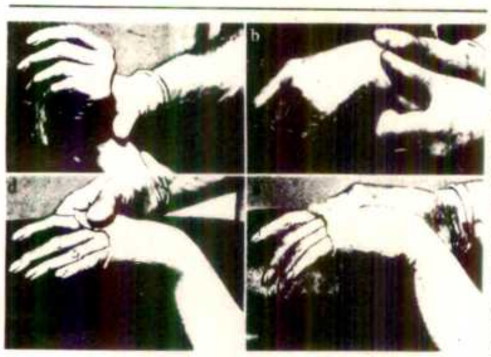

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Br. J. Surg. 1989, Vol. 76, May, 427–428

Current indications for elective peptic ulcer surgery

Confusion exists over the role of elective surgery in the treatment of chronic duodenal ulcer. Many fewer operations are being performed and some have questioned whether there is any place for surgery for the uncomplicated ulcer.

Highly effective ulcer healing drugs are now available. Five H_2-receptor antagonists exist with more in the pipeline, De-Nol® (Brocades, West Byfleet, UK) and sucralfate are just as effective, and if any ulcer defies such an armamentarium, omeprazole will certainly heal it.

It is not enough merely to heal the ulcer; to alter the diathesis in any way, a permanent reduction in acid output is essential, though to what level is not accurately known. None of the available drugs alter the ulcer diathesis. Although a 2-month course of an H_2-receptor antagonist will heal 90 per cent of ulcers, most of these will recur within 1 year of stopping therapy and even on maintenance therapy the relapse rate is 2·5 per cent per month or 30 per cent per year. Within a day or so of stopping therapy gastric secretion returns to pretreatment levels.

In the 10 years that H_2-receptor antagonists have been available and prescribed in vast amounts there has been no reduction in ulcer mortality rate. Indeed in the last few years the number of deaths from peptic ulcer in England and Wales has increased and this is most marked in those over the age of 65 years[1]. The major complications of peptic ulceration, namely bleeding and perforation, now account for over 4500 deaths annually and in devising a strategy for treating peptic ulceration this consideration must be paramount. We can only reduce ulcer mortality by preventing these complications and if it is well recognized that they are most dangerous in the elderly. Indeed, 95 per cent of ulcer deaths occur in patients over the age of 55 years, the mean age in fatal cases being 71 years[1]. Clearly the widespread use of H_2-receptor antagonists is having no effect on ulcer mortality because most ulcers recur unless long term, often lifelong, full dose treatment is embarked upon. Some patients even develop bleeding or perforation while taking these drugs. A significant minority of ulcers occur in those without an established ulcer diathesis and without any previous dyspepsia; clearly nothing can be done, either medically or surgically, to prevent these asymptomatic ulcers from bleeding or perforating. Most patients who develop bleeding or perforation, however, have a history of a well established ulcer diathesis. It has been shown by Pulvertaft[2] that between the ages of 50 and 60 years, patients with chronic peptic ulceration run a 25 per cent risk of bleeding and a 10 per cent risk of perforation. The incidence of these complications increases over subsequent decades. The mortality rate after a bleed from a peptic ulcer remains today, as it has throughout this century, at 10 per cent, and the mortality rate for perforation is in excess of this, at approximately 12 per cent[3].

In elderly patients there is certainly no evidence that the widespread use of H_2-receptor antagonists is reducing mortality. The slight increase in mortality rate already referred to is, paradoxically, occurring at a time when the prevalence of peptic ulcer, the hospitalization of ulcer patients and the use of elective surgery have all declined dramatically.

The evidence does not exist to attribute this increased mortality to the reduction in the number of ulcer operations but this may be a factor. The other major potential factor, namely the use of non-steroidal anti-inflammatory drugs, has recently been called into question by an Australian case controlled study[4] which showed that neither aspirin nor other non-steroidal anti-inflammatory drugs were associated with increased case fatality rates from peptic ulceration. Although these drugs produce symptoms in patients with peptic ulceration, we do not know whether they cause ulcers; similarly we do not know whether H_2-receptor antagonists and other drugs, including prostaglandins, are protective and they probably are not. Vagotomy and other operations for peptic ulceration probably are to some extent protective, for though ulcers may recur after surgery these rarely bleed or perforate[5,6].

The risk of mortality after peptic ulcer surgery has fallen significantly in recent years, in particular with the introduction of highly selective vagotomy. The mortality rates for this operation and for anterior lesser curve seromyotomy with posterior truncal

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vagotomy are 0·3 per cent and 0·16 per cent respectively[7,8]. Recurrence rates between 14 and 18 years after highly selective vagotomy are worrying, they are reported to be 30 per cent in the longest term study. Even so, none of these recurrent ulcers has bled or perforated although 30 per cent of the patients had bled preoperatively[5]. Thus, recurrent ulcers after highly selective vagotomy, while highly undesirable, are rarely if ever life threatening.

If peptic ulcers are treated by the more radical operation of truncal vagotomy and antrectomy, the operative mortality rate and recurrent ulcer rate are both about 1 per cent. Small and his colleagues[6] carried out a long term study on 779 men with peptic ulcers treated surgically between 1947 and 1965 with a minimum follow-up of 15 years. Of the 360 deaths that had occurred none was related to peptic ulceration. Thus after peptic ulcer surgery people do not die from peptic ulcer complications.

In those patients with an established chronic ulcer diathesis, a condition developing in most before the age of 40 years[2], potentially fatal bleeding or perforation can therefore be prevented by elective peptic ulcer surgery which is extremely safe. On the other hand, up to the age of 50 years, peptic ulceration is not a life-threatening condition and no one should undergo surgery for this condition unless it can be shown to be beneficial, not only be relieving symptoms but also by reducing the risk of mortality. After all it was to prevent potentially fatal complications that ulcer surgery was initially promulgated before the First World War. The attitude towards elective ulcer surgery could be similar to that adopted in ulcerative colitis where operative treatment is used to prevent fatality from either perforation or malignancy. Here one operates on patients with an aggressive form of the disease which fails to respond to repeated courses of medical therapy and long term maintenance therapy and also on those with a history of 20 or more years of active disease. In this way, mortality from ulcerative colitis has been reduced and it is possible that surgery has the same potential in the ulcer diathesis.

To establish guidelines, one could recommend ulcer surgery for those who frequently relapse on maintenance therapy with H_2-receptor antagonists, relapse early after three or more 2-month courses of these drugs, and those who have relapsed after three or more courses of the drug at or about the age of 50 years. This last criterion would probably provide the largest group of patients who, on undergoing surgery at that age, would still benefit from the low mortality risk of pylorus preserving ulcer surgery, would have negligible morbidity in terms of dumping and diarrhoea, and would have an extremely low incidence of perforation or bleeding even if they developed a recurrent ulcer. The only alternative strategy over the age of 50 years would be life long continuous full dosage H_2-receptor antagonist therapy with the attendant problems of lack of compliance and ever-increasing cost. Employing this relatively conservative surgical strategy one could save large amounts of money in drug costs and transfusion requirements and significantly reduce the risk of mortality in the patient with an established ulcer diathesis.

T. V. Taylor

Manchester Royal Infirmary
Manchester M13 9WL
UK

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Br. J. Surg. 1989, Vol. 76, May, 429–430

Changing concepts in renovascular surgery

The kidney is an organ with exocrine as well as endocrine functions. The most well known endocrine function is renin production by the juxtaglomerular cells; renin is a proteolytic enzyme which interacts with angiotensinogen to form angiotensin I. A converting enzyme then produces the octapeptide angiotensin II, a potent vasopressor. A low blood pressure, such as that produced by a marked renal artery stenosis, causes increased renin secretion and thereby hypertension. When only one side is affected, nephrectomy can be used to treat the hypertension as first demonstrated by Howard *et al.* in 1954[1]. The sacrifice of renal parenchyma could, however, be accepted only if a good result could be predicted with regard to blood pressure control, and if the patient had a well functioning contralateral kidney.

With the advancement of reconstructive vascular surgery, nephrectomy soon became obsolete as a treatment for renovascular hypertension and was replaced by vascular reconstruction[2]. New, potent antihypertensive drugs have, however, offered strong competition to renovascular surgery. Today, this type of surgery must be effective, reliable and free from undue risks, in order to be an acceptable alternative in the treatment of renovascular hypertension.

There is, however, still a strong case for renovascular surgery, but the indication is now different. Antihypertensive medication, although valuable in the care of the hypertensive population, cannot prevent the progress of the arteriosclerotic disease. The decreasing renal blood flow, caused by progressive stenosis, impairs exocrine kidney function. The end point of this process is thrombotic occlusion of the stenotic renal artery. The main current indication for renovascular surgery, at least in arteriosclerotic disease, is therefore not to decrease blood pressure but to preserve and restore renal function.

The risk of an arteriosclerotic renal artery stenosis progressing to occlusion is quite high in contrast to that of stenosis caused by fibrous dysplasia. In various reports, between 10 and 17 per cent of arteriosclerotic renal artery stenoses have been found to occlude within 2–3 years[3,4,5]. It has also been reported that about 40 per cent of patients with one-sided arteriosclerotic renal artery stenosis develop contralateral stenosis within 52 months[4].

Can we predict which renal arteries with arteriosclerotic stenosis will occlude? We have recently studied 24 patients, whose stenotic arteries have occluded during work-up, or during efforts to treat the patients conservatively[6] (H. Weibull *et al.*, unpublished results). These were compared with a series of patients whose stenotic arteries remained patent for a similar length of time.

Although it is difficult to predict occlusion in individual patients, there are clear differences between the two groups: the group that occluded were significantly older (median age 64 *versus* 55 years), had narrower stenosis (1·0 *versus* 1·5 mm), and had more advanced generalized arteriosclerosis, including contralateral renal artery stenosis (50 *versus* 9 per cent) and ischaemic heart disease (90 *versus* 70 per cent). These patients obviously also represent a high-risk group from a surgical point of view.

Can we diagnose the occlusion once it occurs? It is well known that acute occlusion of a non-stenotic artery, due to embolus or trauma, often but not always causes flank pain as a sign of partial or complete renal infarction[6]. Urine output may decrease and serum creatinine rise, but this is not marked if the contralateral kidney is functioning well. Occlusion as the end result of renal artery stenosis is more difficult to detect. In our series of 24 patients, where we had a relatively limited period during which a stenotic renal artery is known to have occluded, all patients had indeed some signs or symptoms, although they were usually vague and therefore overlooked. The most important sign was a slight but significant rise in serum creatinine (in 23 patients), indicating impaired kidney function also on the contralateral side. Furthermore, a decrease in the length of the kidney was a regular finding. Flank pain was found in five of the 24 patients, shortness of breath in four, malaise in four, fatigue in three and headache in two.

In the light of this knowledge: which patients should be treated actively, and what type of active treatment should we choose, surgical reconstruction or percutaneous transluminal angioplasty?

It is technically easier, and the results are better, when a stenotic but patent renal artery is reconstructed as opposed to an occluded one. This should favour an active, prophylactic attitude being adopted towards the group of patients who are at high risk of renal artery occlusion. They also belong, however, to a high-risk group from

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a surgical point of view, and many factors have to be considered before we advise these patients to undergo major surgery. Knowledge of the high risk of occlusion in certain types of patients is, however, important when discussing the indications to operate on patients with renal artery stenosis.

The management of the patient with an occluded renal artery is no less difficult. Occlusion of a non-stenotic renal artery, due to embolus or trauma, often results in a renal infarct. In order to save such a kidney it is necessary to intervene within 24 h by embolectomy, induced thrombolysis or vascular reconstruction[7]. When a previously stenotic renal artery occludes, the situation is quite different. Collaterals have usually developed and preserve kidney viability. As the symptoms are vague, the diagnosis is often overlooked or made, often accidentally, a long time after the occlusion. In our handling of these patients we have several options[8]. If there is a well functioning kidney on the contralateral side, we may choose to do nothing, or, if there is a reasonably severe hypertension, we may remove the kidney with the occluded artery. If there are any problems with the kidney or renal artery on the contralateral side, we should, however, make every effort to revascularize the kidney on the occluded side. Unfortunately, there are no reliable ways to predict success in these cases[5,9,10]. Unfavourable factors are: small size of the kidney (less than about 9 cm in length), poor visualization of the kidney in the nephrographic phase, no excretion of contrast medium, and no filling of the renal artery distal to the occlusion. A long interval between occlusion and revascularization probably also decreases the chance for success, but this time is often unknown. Preoperative renal biopsy does not seem to be of any help. Although the risk of failure of a reconstruction is higher in occluded cases than stenotic ones, the success is sometimes remarkable, with retrieval of function that has been lost for several weeks. This is important for patients in an age group where chronic dialysis is not an attractive alternative[9].

Regarding the choice of method for revascularization, reconstructive vascular surgery or percutaneous transluminal angioplasty (PTA), there is a wide difference of opinion. Satisfactory results of PTA have been reported in patients with fibromuscular disease[11], but the results have been more disappointing in patients with arteriosclerotic lesions, especially those involving the aortic ostium of the renal artery[12]. In these patients there is a high risk of initial failure, and of early recurrence of the stenosis. We have been particularly disappointed with PTA in patients with a severely ischaemic kidney and impaired excretory function. Even after successful dilatation, there has sometimes been permanent damage to the renal parenchyma, possibly caused by injection of contrast medium in the ischaemic kidney during the procedure[13]. A prospective, randomized study, comparing reconstructive surgery and PTA, is now being performed at our institution and will, we hope, throw some light on this difficult problem.

S.-E. Bergentz
D. Bergqvist
H. Weibull

Malmö General Hospital
S-214 01 Malmö
Sweden

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Br. J. Surg. 1989, Vol. 76, May, 431–434

Sequelae of internal sphincterotomy for chronic fissure in ano

I. T. Khubchandani and J. F. Reed

The HealthEast Teaching Hospital (The Allentown Hospital – Lehigh Valley Hospital Center), 1200 South Cedar Crest Boulevard, Allentown, Pennsylvania 18103, USA

Correspondence to:
Professor I. T. Khubchandani, 1275 South Cedar Crest Boulevard, Allentown, Pennsylvania 18103, USA

A total of 1355 patients underwent internal sphincterotomy for chronic fissure in ano *between 1980 and 1985. Surgical data were obtained for 1102 patients, and 829 patients responded to a questionnaire. Of the 1057 for whom the time of healing was recorded, 1033 (97·7 per cent) healed by a mean time of 5·6 weeks. No significant differences in satisfaction with the outcome or in deficits in continence were noted between groups undergoing lateral, bilateral or posterior midline sphincterotomy. Excision of the fissure was found to be unnecessary. According to responses on the questionnaires, deficits in continence ranging from 'sometimes' to 'frequently' included lack of control of flatus (35·1 per cent), soiling of underclothing (22·0 per cent) and accidental bowel movements (5·3 per cent). A significantly higher proportion of patients who had accidental bowel movements were aged over 40 years.*

Keywords: Internal sphincterotomy, anal fissure, continence

The surgical treatment of chronic fissure *in ano* has evolved, in accordance with the thesis of hypertonicity of the internal sphincter, to procedures that temporarily or permanently decrease or eliminate the spasm in the internal sphincter. Although sphincter stretch accomplishes healing of the fissure[1,2], its simplicity is marred by the consequences of uncontrolled sphincter dilatation and ecchymoses with resultant fibrosis. The procedure has been modified from the original uncontrolled sphincter stretch under general anaesthesia to a controlled insertion of four fingers for a period of 4 min. The high incidence of disturbance of anal continence and the recurrence rate of 16 per cent[3] have resulted in the unpopularity of this procedure.

Recent manometric studies of the anal sphincter in normal individuals and fissure patients demonstrate an underlying sphincter anomaly that results in the occurrence and persistence of anal fissure. Nothmann and Schuster[4] recorded increased resting pressure of the anal sphincter in patients with anal fissure. They found that the abrupt relaxation of the internal sphincter in response to rectal distension does not gradually diminish with a return to base-line pressure as it normally should. Instead, the period of relaxation is followed by a significant and prolonged contraction of the anal sphincter to higher than initial base-line levels. This characteristic 'overshoot' response was seen in 90 per cent of the fissure patients compared with 26 per cent of normal subjects. The overshoot phenomenon disappears temporarily after sphincter stretch treatment of fissure. The normal resting pressure is evidently maintained longer after surgical sphincterotomy.

Eisenhammer[5,6] described lateral internal sphincterotomy for the treatment of anal fissure. Although Notaras[7] is generally credited with having first performed subcutaneous lateral sphincterotomy, Ribeiro[8] described the technique in 112 patients in 1960. Controversy still exists regarding minor variations in technique and differences in effectiveness between posterior midline, unilateral, and bilateral sphincterotomy; subcutaneous *versus* open sphincterotomy; excision, 'landscaping' (excision of proximal papilla and distal anal tag without excising the fissure), or fissurectomy; and local, general or regional anaesthesia.

A total of 1355 patients with chronic fissure *in ano* were treated by sphincterotomy at HealthEast Teaching Hospitals over a 5-year period. The data were analysed to determine the extent to which sphincterotomy resulted in long-term defects in continence, and whether sequelae differed according to the type of sphincterotomy performed.

Patients and methods

Questionnaires were mailed to 1355 patients who had undergone surgery for chronic fissure *in ano* between 1980 and 1985 Chronic fissure *in ano* was defined by a history of more than 4 weeks of symptoms and the appearance of chronicity with lack of oedema, evidence of scar tissue at the edges of the raw area, and the visibility of internal sphincter fibres in the base of the ulcer.

Responses were received from 829 patients (61·2 per cent), and surgical data were obtained from co-operating physicians for 1102 (81·3 per cent) of the total population. Matching surveys with respective surgery data yielded a common subset of 717 subjects (52·9 per cent). In the larger group there were 642 female and 460 male patients ranging in age from 14 to 89 years (mean 42 8 years). Bleeding (72·6 per cent), itching (34·9 per cent), burning (33·0 per cent), protrusion (24·3 per cent) and pain (23·5 per cent) were the most common symptoms Of the total group, 16·4 per cent had undergone previous anorectal surgery, and 3 1 per cent had had previous surgery for fissure *in ano* Inflammatory bowel disease was identified in seven patients and diabetes in 18.

The distribution of gender and location of the fissure as assessed from surgical data is shown in *Table 1*. In the records of 25 patients the location of the fissure was not noted. As expected, anterior fissures were more frequent in female patients (18·3 per cent). Severe stenosis was present in 7 1 per cent of the patients, moderate stenosis in 16·9 per cent, and minimal stenosis in 76·0 per cent The criteria for degree of stenoses were subjective, according to the surgeon's evaluation, but inability to insert even the smallest dimension Hill–Ferguson retractor at the time of surgery (following infiltration of local anaesthesia) was the objective criterion for severe stenosis.

Associated haemorrhoidal disease was present in the majority of the patients (93·4 per cent). Of the 1077 patients with full surgical data, 347 (32·2 per cent) had a distal sentinel tag, 210 (19·5 per cent) had proximal hypertrophic papilla, and 107 (9·9 per cent) had bridged-over skin forming a 'fistula'.

The type of sphincterotomy performed is shown in *Table 2*. In 126 of the 1102 cases with surgical data the type of sphincterotomy was not

Table 1 *Location of fissure*

Location	Total	Male	Female
Anterior	271	74 (6·9)	197 (18 3)
Posterior	668	332 (30·8)	336 (31·2)
Right lateral	11	4 (0·4)	7 (0 6)
Left lateral	5	2 (0·2)	3 (0·3)
Multiple	122	47 (4·4)	75 (7·0)
Total	1077	459 (42 6)	618 (57·4)

Values in parentheses are percentages

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defined. The majority of the patients (49·3 per cent) had bilateral internal sphincterotomy, 62·6 per cent of which were performed by open technique. The associated haemorrhoidal pathology was excised and the wounds were closed completely with 5·0 polyglycolic acid suture. The operation was performed with local anaesthesia in the jack-knife position, as described previously by the authors[9]. The type of sphincterotomy (and the degree) was performed according to the personal preference of each of the five operating surgeons. It was the generally accepted practice that a large Hill–Ferguson retractor could be inserted comfortably into the anal canal at the conclusion of the procedure. Although subcutaneous sphincterotomy has been advocated as a therapeutic alternative[10], we did not employ this technique as a primary method of treatment.

A majority of the patients were discharged from the hospital after an overnight stay. An early bowel movement was encouraged and induced with four tablets of Dulcolax* (Boehringer–Ingelheim Ltd., Ridgefield, Connecticut, USA) administered the evening of surgery.

Table 2 *Type of sphincterotomy*

	Open	Closed	Total	%
Left lateral	230	84	314	32·2
Right lateral	62	44	106	10·9
Bilateral	301	180	481	49·3
Posterior	75	0	75	7·6
Total	668	308	976	100·0

Table 3 *Healing of excised and non-excised fissures*

	Healing			
	Satisfactory	Unsatisfactory*	Total	χ^2 value
Fissure excised				
Closed	490	12	502	0·46†
Trimmed	32	2	34	
Total	522	14	536	
Fissure not excised				
Trimmed	215	3	218	0·32‡
Not trimmed	288	6	294	
Total	503	9	512	

*One patient with unsatisfactory healing had missing excision data, †$P=0\cdot79$, ‡$P=0\cdot24$ (closed *versus* trimmed)

Results

Healing time was noted in the case notes of 1057 patients: 1033 fissures (97·7 per cent) healed satisfactorily taking a mean time of 5·6 weeks. Of the 24 patients with unsatisfactory healing, three underwent reoperation after 12, 14 and 50 weeks: two had deeper sphincterotomies, and one had a posterior sliding graft[11]. Fifteen patients with delayed healing who chose not to have further surgery subsequently healed over a period of 26–78 weeks. Six patients were lost to follow-up.

χ^2 analyses showed that there were no significant differences in healing between the various types of sphincterotomies performed ($\chi^2=2\cdot74$, $P=0\cdot50$) or between fissures that were excised or not excised ($\chi^2=0\cdot55$, $P=0\cdot76$; *Table 3*). Of the 536 fissures that were excised, χ^2 analysis showed no difference in healing between excision of the fissure *versus* 'trimming' without fissurectomy (χ^2 (with Yates' correction)$=0\cdot46$, $P=0\cdot79$). Of the 512 patients whose fissures were not excised, there was no difference in healing between those trimmed or not trimmed ($\chi^2=0\cdot32$, $P=0\cdot24$). Excision data were missing from 54 records.

Continence

Deficits in continence according to type of sphincterotomy performed are shown in *Table 4*. χ^2 analyses showed no differences between sphincterotomies in terms of lack of control of gas, soiling of underclothing, or accidental bowel movements. The responses on 829 questionnaires involving defects in continence and gender were analysed (*Table 5*). Overall, 35·1 per cent of the patients complained of lack of control of gas ranging from 'sometimes' to 'frequently'. No difference in control of gas was experienced according to gender. Twenty-two per cent of the patients admitted to soiling of underclothing 'sometimes' to 'frequently'. Men reported a significantly higher incidence of soiling (32·7 per cent) then did women (14·0 per cent). An alarming 5·3 per cent of the patients complained of accidental bowel movements for which 4·0 per cent regularly wore absorbent pads. However, only 56 patients (7·8 per cent) responded that they were extremely dissatisfied or not very satisfied with the outcome of their surgery (*Table 6*). Of the 21 male patients who complained of accidental bowel movements 15 were older than 40 years, of the 23 female patients with this problem, 17 were also in that age category. χ^2 analysis showed that there was a significantly higher proportion of patients aged over 40 years who were suffering from accidental bowel movements ($\chi^2=5\cdot2$, $P<0\cdot02$).

Table 4 *Deficits in continence by type of sphincterotomy performed*

	Type of sphincterotomy				
	Left lateral	Right lateral	Bilateral	Posterior	Total
Lack of control of gas					
Frequent/often	17	6	33	2	58
Sometimes	64	23	94	16	197
Rarely/never	136	47	237	40	460
Total	217	76	364	58*	715‡
Soiling of underclothing					
Frequent/often	18	5	21	2	46
Sometimes	24	17	53	12	106
Rarely/never	174	54	290	46	564
Total	216†	76	364	60	716§
Accidental bowel movements					
Frequent/often	1	1	0	0	2
Sometimes	10	5	15	3	33
Rarely/never	205	70	349	57	681
Total	216†	76	364	60	716‖

*2 missing records; †missing record. ‡$\chi^2=3\cdot28$, $P=0\cdot77$, §$\chi^2=9\cdot13$, $P=0\cdot17$; ‖$\chi^2=5\cdot31$, $P=0\cdot50$ (four types of sphincterotomy and three levels of frequency compared)

Table 5 *Deficits in continence by gender*

	Total	Male	Female
Lack of control of gas			
Frequent/often	72 (8·7)	30 (8.5)	42 (8·8)
Sometimes	219 (26·4)	90 (25·6)	129 (27·0)
Rarely/never	538 (64·9)	232 (65·9)	306 (64·2)
Soiling of underclothing			
Frequent/often	63 (7·6)	51 (14·5)	12 (2·5)
Sometimes	119 (14·4)	64 (18·2)	55 (11·5)
Rarely/never	6747 (78·0)	237 (67·3)	410 (86·0)
Accidental bowel movements			
Frequent/often	3 (0·4)	2 (0·6)	1 (0·2)
Sometimes	41 (4·9)	19 (5·4)	22 (4·6)
Rarely/never	785 (94·7)	331 (94·0)	454 (95·2)
Total	829	352	477

Values in parentheses are percentages

As many as 42 per cent of the respondents (50 per cent of men and 36 per cent of women) admitted to their bowels being 'loose', ranging from 'sometimes' to 'frequently' It was suggested that poor diet, beer drinking habits and history of loose bowels may very well forewarn against a poor outcome of sphincterotomy for treatment of fissure *in ano*.

Discussion

If it is the assumption that internal sphincterotomy is the procedure of choice in the management of chronic fissure *in ano*, the debate should logically address not only the result in terms of healing of the fissure but also the overall impairment of physiology and its social consequences. Varying degrees of incontinence following lateral internal sphincterotomy have been reported in the literature. Vafai and Mann[12] reported an incidence of 1 per cent permanent partial incontinence for faeces after closed lateral internal sphincterotomy under local anaesthesia in 702 patients. Bailey *et al.*[13] reported an incidence of incontinence of 1 per cent for gas and 1·2 per cent for faeces in an evaluation of 418 patients who had lateral internal sphincterotomy performed. Six of the 99 patients interviewed by Hoffmann and Goligher[3] were unable to control flatus satisfactorily, and one had additional occasional incontinence for faeces. Walker *et al.*[14] conducted a long-term follow-up (mean 4·3 years) on 100 patients who had undergone internal sphincterotomy for anal fissure and stenosis. Fifteen per cent showed minor defects in continence, but none had faecal soiling severe enough to require a pad. The reported incidence of incontinence in other reports[15–17] ranges from 3 to 50 per cent.

This survey and others have reported a disturbingly high incidence of permanent incontinence. Could the ill effects be lessened or eliminated by attention to operative technique? Eisenhammer[6] warned particularly against division of more than the lower half of the internal sphincter, but Bennett and Goligher[17] found that frequency of such disorders was little affected by extent of the sphincterotomy. Bennett and Duthie[18] thought that the relatively insensitive furrow in the posterior midline following sphincerotomy allowed faecal matter to escape surreptitiously from the rectum to the exterior without evoking the normal sphincter response Unfortunately, a high incidence of defect in continence also results following bilateral internal sphincterotomy. The pelvic floor physiology laboratory at our institution is now studying the pre- and postoperative functional abnormalities of the internal sphincter following surgical division of a large bulk of the internal sphincters. Central to the unresolved questions are the issues discussed below.

Does the fissure have to be excised?

The results of the present study suggest that it is not necessary to excise the fissure. It might even be suggested that excision of the fissure with creation of a fresh surgical defect is undesirable. We found there to be no difference in healing between the patients with excised and non-excised fissures. Indeed, of the 288 patients for whom the fissure was neither excised nor trimmed, only six had prolonged healing (*Table 3*).

Table 6 *Satisfaction with the outcome of surgery by type of sphincterotomy*

	Type of sphincterotomy				
	Left lateral	Right lateral	Bilateral	Posterior	Total
Extremely/very satisfied	134	56	256	44	490
Satisfied	65	15	76	12	168
Extremely/very dissatisfied	18	4	30	4	56
Total	217	75*	362†	60	714

*missing record; †missing records; $\chi^2=8{\cdot}68$, $P=0{\cdot}19$ (four types of sphincterotomy and three levels of satisfaction/dissatisfaction compared)

Unilateral/bilateral sphincterotomy versus *posterior midline sphincterotomy*

Posterior sphincterotomies were performed in 60 patients from the subset of 717 whose operative reports specifically described nature of the procedure and who responded to the questionnaire (*Table 4*). There were no statistically significant differences in continence or ultimate outcome among any of the sphincterotomy types. Bilateral sphincterotomy was performed on approximately 50 per cent of the patients.

Subcutaneous versus *open sphincterotomy*

In this series, subcutaneous sphincterotomy was performed on one side only in conjunction with open sphincterotomy on the other. Therefore no valid conclusions can be drawn. Reports in the literature attest to the effectiveness of subcutaneous sphincterotomy[10]. It does not eliminate, however, the associated pathology present in the majority of patients presenting with fissure *in ano*.

Local versus *general anaesthesia*

Although there are studies claiming the superiority of general anaesthesia for the performance of subcutaneous sphincterotomy[19], in our experience with a vast number of anorectal procedures, adequate procedure may be performed with local anaesthesia, particularly if the jack-knife position is preferred.

Internal sphincterotomy in the management of fissure *in ano* is clearly safe and effective, but is often associated with disturbing consequences of deficit of continence. Particular caution in the depth and the length of sphincterotomy performed, especially in patients over 40 years of age, may be necessary. Perhaps a routine preoperative manometric study could accurately determine the extent of sphincterotomy to be performed.

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Announcement

Association of Surgeons in Training

Membership of the Association is open to all senior registrars holding accredited posts in general surgery, urology, plastic surgery, neurosurgery, orthopaedics, cardiothoracic surgery and paediatric surgery. Registrars in the above specialties who are 2 years post-fellowship may also apply. The Association represents the views of members on all matters relevant to surgical training besides holding scientific and social meetings. If you are not a member please contact the Secretary, Andrew McIrvine, 35, Elsie Road, Dulwich, London SE22 8DX, for details of membership, local representatives and forthcoming meetings. The next AGM will be held in Cardiff from 21–23 September 1989.

For debate

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Obstacles to organ donation

R. E. Wakeford and R. Stepney*

*Cambridge University School of Clinical Medicine, Addenbrooke's Hospital, and *14 Edward Street, Cambridge, UK*

Correspondence to:
Mr R. E. Wakeford, Office of the Regius Professor of Physic, Cambridge University School of Clinical Medicine, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

Attitudes towards transplantation were investigated in national surveys of the general public (n=*1471*)*, the medical profession* (n=*590*) *and key clinical staff in units referring potential organ donors* (n=*380*)*. A clear majority of doctors would like to see more transplants. Only 16 per cent of doctors opposed them on cost grounds, and a 50 per cent 5-year survival rate is seen as more than adequate clinical justification. However, doctors are less supportive of liver and heart grafts than of kidney and cornea grafts. Few lay people would refuse donation of specific organs, but 30 per cent worry that doctors might be pressured into removal of organs when they are not sure the patient is dead. Religious or moral objection is rare. Intensive care unit staff felt the most important factor restricting organ harvest in their own units was dislike of adding to relatives' distress, followed by lack of training in approaching relatives and adverse media publicity. Only 11 per cent thought reservations on brain stem death a likely or possible influence. Enhanced public awareness of the need for transplants was seen as the most important means of increasing organ harvest. Required request would be controversial and perhaps impossible to implement. We conclude that the time, effort and expense involved in potential organ donation do not play a substantial part in limiting referral. Neither do reservations about brain stem death. Increased training of staff* (*both in communication skills and in the professional responsibility to encourage donation*) *and greater public awareness are seen as the twin foundations of a realistic approach to enhancing referral.*

Keywords: Organ procurement, transplantation, attitude of health personnel, public opinion, medical education

An estimated 3500 patients are awaiting renal transplants, and waiting lists for heart and liver transplants and corneal grafts have doubled in the past 2 years[1]. Particularly in the case of renal transplants, it is widely accepted that these delays are due to a shortage of organs (rather than to limited facilities) and that much of the shortfall in organs could be met if more medically eligible brain stem dead patients were referred as potential organ donors[1–5].

In 1981, it was calculated that 4000 cases of brain stem death occurred each year in the UK, yet there were only 1000 renal transplants[4]. A more recent 3-year study[2] of brain stem dead patients in Nottingham showed that in the area covered by the transplant unit 50 kidneys per 10^6 population per year were suitable for transplantation, but that only half of the patients were being referred for kidney retrieval. Ninety of the 105 patients diagnosed as brain stem dead during the study were judged suitable for liver donation and 71 for heart donation, yet only five livers and 14 hearts were recovered. In 6 months of prospective study, organs from six brain stem dead donors were used, while organs from nine potential donors were not; in two cases relatives were not approached, while in seven cases relatives were approached but refused consent. Although medical staff were more likely to broach the subject of organ donation than a decade earlier[3], lack of policy on who should approach relatives was thought to be implicated in this high rate of loss.

Given wide variations in organ procurement from hospitals with similar patient populations, and from the same hospital in different years as staff change, Jennett and Hessett[4] argued that doctors' reluctance to initiate donation, rather than the refusal of relatives, was the important factor underlying poor rates of organ harvest

The Conference of Medical Royal Colleges and their Faculties has recently reported on the supply of donor organs for transplantation[1]. The report suggested a number of possible reasons for the shortfall in organs: lack of medical experience and knowledge, doubts about the success of transplants and the brain stem death criteria, demand for intensive care unit (ICU) beds, time constraints (including in theatre), cost, and medicolegal constraints During the preparation of the report, a questionnaire was sent to all ICUs. However, the survey had to be conducted quickly, so that only 108 replies were received (about a 37 per cent response rate), and no data derived from the questionnaire were presented

We undertook a large-scale survey of staff working in intensive care and related units. Its aim was to identify the obstacles to increased organ harvest, as seen by those most directly involved in referring potential donors, and to obtain their views on suggested changes in the way consent for organ donation is obtained. However, it is clear that the availability of organs for transplantation is affected by the views of the wider medical community and also, crucially, by public attitudes. The questionnaire study of intensive care staff was therefore complemented by surveys of public and professional opinion. All three surveys were conducted in November and December 1987.

Methods

The surveys

The general public survey Questions relating to transplantation were included in an 'omnibus' public opinion poll (conducted by Research International Medical Research/Marplan). In all, 1471 people, a representative national sample of the adult population in

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the UK, were interviewed. Respondents were first asked whether their general practitioner (GP) had raised the matter of organ donation with them, and if they would like him/her to do so Other questions concerned: attitudes towards transplantation generally and to specific organ transplants, beliefs about doctors' ability to diagnose death accurately (and their response in this situation to medical colleagues pressurizing them to make this diagnosis), and possible changes to the rules surrounding organ donation (the introduction of 'opt in', 'opt out' or 'required request')

The medical profession survey. Two random samples of doctors were drawn from the files of the mailing agency used by the Department of Health to contact all doctors. The first consisted of 250 GP principals, and the second sample consisted of 750 hospital doctors in the National Health Service (NHS) at registrar grade and above The sample of hospital doctors was larger to allow breakdown by general specialty.

These 1000 doctors were sent an explanatory letter accompanying a nine-item questionnaire covering attitudes towards transplantation in general and towards the transplantation of specific organs The statements with which respondents were asked to agree or disagree (anonymously) covered potential religious/moral, clinical and financial objections Responses were analysed for the group as a whole and (using the χ^2 test) by gender, age and specialty. We report differences significant at $P<0.02$

Medical and nursing intensive care staff survey. After discussions with three regional transplant co-ordinators, pilot telephone interviews were conducted with ten senior medical and nursing staff from five ICUs judged representative of different types of hospital The semistructured interviews explored attitudes towards referral of potential organ donors and possible obstacles to increasing the yield of organs The information obtained was used in designing an anonymous postal questionnaire

Two questionnaires were sent to each general, neurosurgical and paediatric ICU listed in the 1987 Directory of Emergency and Special Care Units[6] Combined ICU and coronary care units were sent questionnaires if their specified interests included head injury, trauma, neurosurgery or 'general'. A total of 590 questionnaires were sent, addressed personally to the senior consultant and the senior nurse in each unit, using names listed in the directory. Questionnaires were not sent to burns or neonatal ICUs, units concerned purely with coronary or postsurgical care, or to accident and emergency departments Respondents gave information on the type of hospital and unit in which they worked

Data have been analysed for the survey population as a whole, and (using the χ^2 test) by staff category (doctor or nurse), type of hospital and type of ICU. We report differences significant at $P<0.02$.

Results

Public attitudes

Only 2 per cent of respondents said that their GP had talked to them about the possibility of donating their organs for transplantation. Twenty-five per cent said that they would like their GP to do so and would value his advice, and a further 27 per cent said they would be prepared for the GP to discuss the matter, although they were not sure it would change anything. Thirty-five per cent regarded the matter as none of the GP's business, and 13 per cent could not answer.

On the question of establishing death after a serious accident, 53 per cent of respondents said they would trust doctors completely to be sure a person was really dead, 28 per cent would trust them but had 'a tiny doubt', 12 per cent were not sure and had major worries, 2 per cent would not trust doctors at all, and 4 per cent did not know. Responses to this question were virtually unchanged when the item was rephrased to ask what people would feel if they themselves had had the accident.

Sixty-three per cent of the sample were sure that doctors would never give permission for the removal of organs unless they were certain the patient was dead, even when under pressure from transplant doctors who needed the organs urgently. However, 30 per cent worried that doctors might sometimes be pressurized in that way Seven per cent answered 'don't know'.

Only 5 per cent of those interviewed said they had any moral or religious objection to the transplantation of organs from a dead person to a live one. Seventy-eight per cent said they would certainly agree to a heart transplant that might save the life of their child; only 5–6 per cent said they would themselves refuse the transplant of a heart, liver, kidney, lung, pancreas or cornea. When it came to having organs taken from them, rates of refusal were marginally greater: 9 per cent for the heart; 7 per cent each for the kidneys, liver and pancreas, and 11 per cent for the cornea.

Twenty-two per cent of the sample said they had a donor card, but only 14 per cent had it with them at the time of the interview. Asked why people did not carry donor cards, 44 per cent suggested it was because they had not thought about donating organs, 24 per cent that they could probably not be bothered, 15 per cent that people might worry about not being completely dead when organs were removed, 9 per cent that they might have moral or religious objections, and 8 per cent because people might think it was tempting fate.

The respondents were asked three questions relating to possible changes in the rules regarding organ donation, aimed at increasing the supply for transplantation. One suggestion dealt with an opt-out system (unless you registered an objection on a central computer, doctors could assume that when you die your organs can be removed, subject to your family's wishes); another involved the opt-in system (people who want to donate their organs should notify a central National Health Service office which would hold their names on a computer, and then they would not need to carry a donor card), a third suggestion involved required request (doctors should be required to ask the relatives of a newly dead patient whether his or her organs might be used for transplantation). Responses are shown in *Table 1*.

Finally, the respondents were asked about the status of a patient's dying request that his or her organs be used, even though relatives disapproved. Seventy-one per cent thought the last request should always be followed, but 17 per cent that it should not be followed if to do so would upset the relatives.

The medical profession

Eighteen questionnaires were returned as undeliverable, and 590 replies were received (60 per cent of those delivered). The response rate for GPs (61 per cent) was similar to that for hospital doctors (59 per cent).

Five per cent of respondents were aged under 30 years, 33 per cent were 30–39 years old, 32 per cent were 40–49 years old, 21 per cent were 50–59 years old, and 9 per cent were aged over 60 years Eighty-six per cent of respondents were men, and 14 per cent were women GPs accounted for 26 per cent of responses; 25 per cent were from doctors in hospital general medicine or medical specialties, 31 per cent from those in surgery or surgical specialties, 9 per cent from doctors working in laboratory or diagnostic specialties, and 7 per cent from those working in other categories.

The overall figures presented are arithmetic means of all responses. GPs, who represent half of all doctors, were deliberately under-represented in the sample drawn. However,

Table 1 *Public attitudes towards suggested changes in rules regarding organ donation*

	Respondents' views of the suggested changes ($n=1471$)				
Suggestion	Very good	Fairly good	Don't know	Fairly bad	Very bad
Opt-out arrangement	465 (32)	350 (24)	316 (21)	155 (11)	180 (12)
Opt-in arrangement	748 (51)	378 (26)	218 (15)	64 (4)	57 (4)
Required request	352 (24)	353 (24)	391 (27)	173 (12)	195 (13)

Less than 1 per cent of interviewees did not respond to each item, values in parentheses are percentages

Table 2 *Attitudes of the medical profession towards organ transplantation in the National Health Service*

Statement	No. responding ($n = 590$)				
	Agree	Tend to agree	Mixed feelings/ don't know	Tend to disagree	Disagree
I would like to see more organ transplantation taking place	361 (61)	137 (23)	60 (10)	17 (3)	15 (3)
I oppose organ transplantation on religious or moral grounds	10 (2)	5 (1)	8 (1)	19 (3)	545 (93)
Organ transplantation is such an important topic that it should be given considerable prominence in undergraduate medical teaching	146 (25)	185 (31)	96 (16)	121 (21)	41 (7)
In general, organ transplantation cannot be justified on practical grounds if 5-year survival rates are only about 50%	17 (3)	54 (9)	73 (12)	189 (32)	255 (43)
Most organ transplantation should be opposed on financial grounds—the NHS would get better value from other approaches or treatments	22 (4)	71 (12)	101 (17)	177 (30)	217 (37)
I support kidney transplants	540 (92)	34 (6)	3 (1)	2 (0)	10 (2)
I support corneal transplants	555 (94)	18 (3)	7 (1)	0 (0)	9 (2)
I support liver transplants	257 (44)	132 (22)	122 (21)	39 (7)	39 (7)
I support heart transplants	269 (46)	123 (21)	110 (19)	47 (8)	40 (7)

*Up to three subjects did not respond to each item; values in parentheses are the percentages of those responding to each statement. NHS, National Health Service

Table 3 *Factors seen as restricting organ harvest in their own units by intensive care unit staff*

Factor	Respondents' views on whether certain factors restrict organ harvest ($n = 380$)		
	Yes	Possibly	No
Dislike of adding to relatives' distress	81 (22)	123 (33)	169 (45)
Reservations about the validity of brain stem death criteria	17 (5)	24 (6)	331 (89)
Lack of clinicians experienced in testing for brain stem death	18 (5)	22 (6)	334 (89)
Resentment at time, effort and expense involved	9 (2)	41 (11)	322 (87)
Lack of training in how to approach relatives	57 (15)	126 (34)	190 (51)
Adverse media publicity about brain stem death/transplant procedures	64 (17)	83 (22)	226 (61)
Unfortunate experiences with transplant teams/members	33 (9)	29 (8)	312 (83)
Lack of unit policies etc. regarding brain stem death and subsequent referral	21 (6)	36 (10)	314 (85)
General distaste on behalf of unit member(s) for the procedures involved in organ harvesting	19 (5)	78 (21)	277 (74)

From six to nine subjects did not respond to each item; values in parentheses are the percentages of those responding to each factor

crudely weighted means do not differ substantially from these means.

Overall figures are shown in *Table 2*. Medical opinion was overwhelmingly in favour of organ transplantation in general. Very few respondents had moral or religious objections. A majority of respondents agreed or tended to agree that transplantation was such an important topic it should be given considerable prominence in undergraduate medical teaching. Fifty per cent 5-year survival is clearly regarded as adequate justification for these views. On balance, doctors strongly supported transplantation on cost grounds.

When asked about specific organs, respondents' support for kidney and corneal transplants was clearly greater than for transplantation of the liver and heart. However, even with liver and heart transplants, the number of respondents voicing full or qualified disagreement was small.

Age was significantly related to attitude to the statement about survival ($P < 0.005$). There was an increase from 7 per cent among those aged under 40 years to 22 per cent in those aged over 60 years in the proportion of respondents agreeing or tending to agree that transplantation would not be justified by 5-year survival rates of 50 per cent. Older practitioners were also more inclined than younger ones to disapprove of heart transplants ($P < 0.005$). Twenty-two per cent of those aged over 60 years fully disagreed or tended to disagree with them, compared with 10 per cent of respondents under 30 years of age and 11 per cent of those aged 30–39 years. There were no significant differences by specialty or gender.

Intensive care staff

Two questionnaires were returned undelivered. Responses were received from 380 people – a 65 per cent response rate Twenty-one per cent were from major teaching hospitals, 27 per cent were from district general hospitals with regional specialties, 46 per cent were from district general hospitals without regional specialties, and 5 per cent were from other types of hospital. Fifty-seven per cent of respondents worked in general ICUs, 25 per cent in mixed ICU and coronary care units, 5 per cent in neurosurgical units, 6 per cent in paediatric ICUs and 7 per cent in other types of unit.

To obtain an early indication of likely responses, questionnaires were sent out in two waves: first to an initial sample of 120 ICUs drawn randomly from the directory and then, 14 days later, to the remainder. Owing to a printing error on the first batch of questionnaires, these respondents were not asked to specify whether they were doctors or nurses. However, this information is known for the 58 per cent of respondents who comprised the second wave; 43 per cent of these respondents were doctors and 57 per cent were nurses.

Factors restricting organ harvest

Respondents were presented with a list of nine factors and asked to say about each whether it restricted the harvesting of organs from their own unit. A choice of three replies (yes, possibly, no) was given.

No single factor was universally accepted as limiting organ harvest (*Table 3*). The factor identified with greatest frequency was dislike of adding to relatives' distress. Next in perceived importance was lack of training in how to approach relatives.

Table 4 *Differences between intensive care unit doctors and nurses in perceived restrictions on organ harvest from their own units*

		Respondents' views on whether certain factors restrict organ harvest (%)		
Factor	Group	Yes	Possibly	No
Lack of training in how to approach relatives*	Doctors	4	33	63
	Nurses	28	31	41
Adverse media publicity about brain stem death/ transplant procedures†	Doctors	13	15	72
	Nurses	19	28	53
Lack of unit policies etc. regarding brain stem death and subsequent referral‡	Doctors	1	9	90
	Nurses	10	11	79

Percentages calculated from a maximum of 213 responses $*\chi^2=21·41$, d.f.=2, $P<0·0001$, $\dagger\chi^2=8·02$, d.f.=2, $P<0·02$, $\ddagger\chi^2=7·85$, d.f.=2, $P<0·02$

Some reasons suggested by initial telephone interviews as potentially important proved not to be so. In particular, there was very little evidence that ICU staff see resentment of the time, effort and expense of organ referral as a disincentive, or that reservations about the validity of brain stem death criteria play a part in discouraging organ harvest.

Analysis of subgroups revealed certain significant differences in opinion between doctors and nurses (*Table 4*). Nurses more than doctors thought lack of training in how to approach relatives restricted organ yield. Similarly, more nurses than doctors thought lack of unit policies on brain stem death and referral limited organ procurement.

There was little suggestion of important differences in attitude between respondents from different types of hospital or unit. However, those respondents who regarded adverse experiences with members of transplant teams as a factor in organ availability were not randomly distributed according to hospital type. Fifteen per cent of respondents from teaching hospitals thought such experiences definitely restricted harvesting in their units, compared with 11 per cent of respondents from district general hospitals with regional specialties and 4 per cent of respondents from other district general hospitals ($P<0·01$).

Developments that might encourage referral of organs

Respondents clearly felt that a number of measures would or might increase referral of potential donors (*Table 5*). 'Enhanced public awareness of the need for transplantation' was the most popular of the five suggestions put to them, followed by encouraging medical and nursing staff to regard referral of organ donors as their duty.

The impact of an opt-in system (in which donor cards would be replaced by a national computer record) and an opt-out system (in which clinicians could assume patients had agreed to organ donation unless they had previously registered an objection) were thought similar in their likely effects on referral. However, the ethical problems posed by an opt-out system were reflected in the fact that 8 per cent of respondents added comments to their reply forms indicating that they would not be prepared to implement such a system.

Required request, whereby doctors are legally obliged to ask relatives of medically eligible patients for permission to use their organs, was also strongly objected to by a significant proportion of respondents. Nineteen respondents (5 per cent of the total) felt strongly enough about the issue to write in comments, eight were hostile to required request ('dangerous', 'disastrous', 'I would refuse to implement such a system', were among the remarks) Nevetheless, more than a quarter of respondents thought required request would increase organ supply, and more than half either thought that it would make no difference or that it might help There was a difference between medical and nursing staff on the issue ($P<0·001$): 36 per cent of nurses thought required request would increase organ yield, but only 17 per cent of doctors did so. Fifty per cent of doctors, compared with 27 per cent of nurses, thought required request would make no difference.

Discussion

While it must be remembered that our data were collected by anonymous questionnaire and must therefore be interpreted with caution, the general survey of medical opinion shows little doubt about the popularity of the transplant programme, although hearts and livers lag behind kidneys and corneas in support. Opinion in favour of transplantation was evenly spread across specialties; there was no evidence, for example, that surgeons were more in favour than physicians, or that hospital staff were more in favour than GPs.

Senior medical and nursing staff who have the opportunity, many would say, the responsibility, to refer brain stem dead patients for organ donation, perceive a number of obstacles to increased rates of referral. Though no single factor stands out as limiting the current harvest of organs, the three factors most frequently seen to be important (dislike of adding to relatives' distress, lack of training in how to approach relatives, and adverse media publicity) all relate to the interaction between the medical profession and the public. There is little suggestion from our data that questions of organization or administration or of medical ethics lie at the root of the organ shortage. In particular, in view of the well publicized objections of individual clinicians[7], it is important to have established that the senior medical and nursing staff who deal with potential organ donors see few problems arising from the validity of current criteria of brain stem death. In the light of authoritative reports[8,9], it appears to be widely accepted by ICU staff that brain stem death invariably heralds asystole. There also appears to be little worry on the part of senior ICU staff about the time, effort and expense of referring potential organ donors. Of course, these are the views of the senior staff involved it is possible that registrars and others who may initiate contact with the transplant team could feel differently, but we were unable, given our resources, to survey them.

Our findings are in broad agreement with those of recent surveys of neurosurgeons and ICU nurses in the USA[10]. Prottas and Batten concluded that reservations regarding the clinical aspects of organ donation are not important factors in limiting organ harvest Of far greater significance is the unwillingness to confront relatives with the diagnosis of brain stem death and the request for permission to harvest organs.

Table 5 *Developments seen by intensive care unit staff as encouraging referral of potential organ donors from their own units*

	No responding (from a maximum of 213)		
	Would help	Might help	Would make no difference
Replacing donor cards by national computer record (opt-in)	96 (26)	146 (40)	126 (34)
System of 'required request'	101 (28)	116 (33)	138 (39)
Enhancing public awareness of the need for transplantation	276 (74)	58 (16)	39 (10)
An opt-out system	102 (29)	108 (31)	140 (40)
General encouragement of medical and nursing staff to regard referring organ donors as their duty	151 (41)	102 (28)	114 (31)

Values in parentheses are the percentages of those responding to each item

In our study, nurses particularly tended to emphasize the importance of adequate training in how to approach relatives. They also emphasized the importance of establishing procedures for arranging organ donation, giving the clear impression that nursing staff in ICUs are less sanguine about the adequacy of present arrangements than are their medical colleagues. This impression also has relevance to one of Prottas' and Batten's conclusions[10]. In this study, neurosurgeons appeared substantially more reluctant than ICU nurses to approach bereaved relatives.

Of the recommendations in the Report of the Royal Colleges[1], we are able to endorse the need for education of the public (in respect of the need for organ donation, as well as about the safety of the brain stem death criteria) and of the medical profession (in communication with bereaved relatives). In relation to public education, there would appear to be a considerable opportunity for GPs to play a major part Regarding doctors, there is now overwhelming evidence that enhancing their communication skills is quite possible[12]. But we also find evidence that the referral of organ donors could be increased if it were accepted by the staff responsible that this was part of their professional duty.

Although a significant proportion of our respondents in ICUs thought that both legally required request and an opt-out system of refusing donation would increase organ harvest, the antipathy shown by others would seem to make both ideas difficult to implement in the UK. It has also been effectively argued on the basis of experience in the USA that required request is likely to make little impact on organ harvest, as ending the physician's discretion in such matters is far more difficult to achieve in practice than in theory[11].

The education of the public regarding the need for organs and the safety of the brain stem death criteria, and of the professionals in communication with bereaved relatives, ought to be relatively straightforward and uncontroversial to arrange. We conclude that this should take precedence over any more coercive measures.

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Adjuvant multimodality treatment of rectal cancer

D. J. Galloway, A. M. Cohen*, B. Shank* and M. A. Friedman†

*University Department of Surgery, Western Infirmary, Glasgow, UK, *Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York and †Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, USA*

Correspondence to:
Dr A. M. Cohen, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York 10021, USA

It has long been recognized that curative surgery as the sole treatment for rectal cancer yields disappointing results. There is now a growing body of evidence from prospective randomized clinical trials to support the role of adjuvant therapy for patients whose primary tumour has spread through the rectal wall or has associated lymph node involvement. Carefully planned radiation therapy with adequate doses and fields can reduce the risk of locoregional failure. Chemotherapeutic agents delivered either systemically or regionally may also contribute to better disease control and survival. A number of diagnostic and therapeutic issues still need to be addressed in order to use the available adjuvant treatment methods most appropriately. Efforts to refine patient selection, to enhance therapeutic effect and to minimize toxicity are likely to improve the outlook for patients with resectable rectal cancer.

Keywords: Rectal cancer, adjuvant therapy, review, randomized prospective clinical trials

Data from a growing number of clinical trials indicate that adjuvant therapy plays an important part in the overall management of patients with resectable rectal cancer Local control and overall survival appear to be enhanced if definitive surgery is combined with irradiation and chemotherapy.

The purpose of this review is to emphasize the limitations of surgery alone in certain subsets of patients with rectal cancer and to examine critically the advantages and disadvantages of adjuvant treatment methods. We also describe the major current trials and suggest areas of future study necessary to address some of the unanswered questions regarding multimodality therapy

Results with surgery alone

Overall survival

The majority of patients (71–93 per cent) with node-negative rectal cancer are cured by radical surgical resection[1–3]. In contrast, only a minority of patients (29–41 per cent) whose rectal cancers have spread to regional lymph nodes are cured by surgery[1–3]

Locoregional failure

Achieving locoregional disease control at the time of primary treatment is of paramount importance Not only can pelvic recurrence lead to disabling symptoms, but treatment of symptomatic recurrence is usually unsatisfactory. It is likely that most cases of pelvic recurrence after radical surgery are related to direct microscopic radial spread[4] and/or intralymphatic tumour cells[5]. The recurrence of pelvic tumour is directly related to the extent of transmural tumour penetration and to the presence of lymph node metastases[6–12]. This is shown in relation to pathological stage in *Figure 1*. Although local recurrence may occur in 22–67 per cent of node-positive patients treated only with surgery, it is frequently accompanied by evidence of distant metastases (10–61 per cent)[6,10–12].

Failure patterns determined at autopsy provide insight into the relative risks of local and distant recurrence. In the series from the Massachusetts General Hospital[6], isolated pelvic recurrences were documented in 25 per cent of patients, but a total of 75 per cent of cancer-related deaths were associated with tumour in the pelvis. These data would suggest that improved local control of the primary cancer and regional nodes may not only reduce cancer-related morbidity but may also improve survival

Distant metastases

The relatively disappointing long-term cancer-specific survival rate after curative surgery has been largely explained by the occurrence of occult metastatic disease In 1941 Goligher studied 790 consecutive rectal cancer patients who were considered to have no metastatic liver disease at the time of laparotomy[13]. Thirty patients died in the immediate postoperative period and at autopsy, five (17 per cent) of these patients had histological evidence of liver metastases. In a more recent study, a group of colorectal cancer patients treated for cure were followed prospectively with frequent liver imaging[14] Within 2 years 29 per cent had developed liver metastases, suggesting that these had been present but undetectable at the time of primary treatment.

Radical surgery and adjuvant irradiation

There is a considerable body of data from non-randomized studies which suggests that adjuvant radiation therapy can reduce the pelvic recurrence rate. While these data cannot be used to provide scientific validation of the usefulness of this

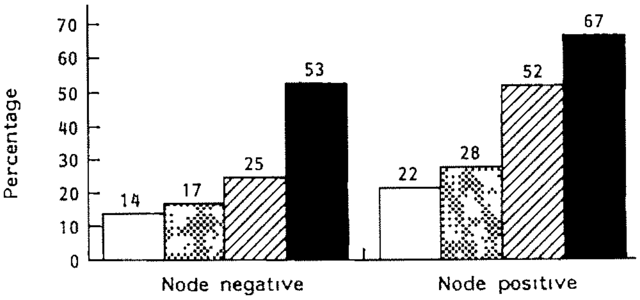

Figure 1 *Pelvic recurrence in rectal cancer related to pathological stage*[6,7]. □, *invasion into muscularis propria (T2);* ▩, *microscopic penetration into perirectal fat (T3m),* ■, *gross penetration into perirectal fat (T3g),* ■, *adherence or invasion into a contiguous structure (T4)*

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Table 1 *Randomized studies of preoperative radiation therapy*

Study	Year of publication	Dose (cGy)	No RT	RT	Local recurrence rate (%)		5-year survival rate (%)	
					No RT	RT	No RT	RT
Princess Margaret Hospital[33]	1977	500	56	55	—	—	35	35 (overall)
							17	35 (Dukes' C)
Medical Research Council[35]	1982	500	275	277	57	55	38	42 (overall)
Medical Research Council	1984	2000	—	272		53		40
Memorial Hospital[31]	1974	2000	414	376	23*	13* (Dukes' C)	65	67 (overall)
Veteran's Administration Surgical Oncology Group I[32]	1975	2000–2500	353	347	36	13 (all)	32	40 (overall)
					40	29 (APR)	28	41 (APR)
Stockholm Rectal Cancer Study Group[18]	1987	2500	343	357	16	7	—	—
Veteran's Administration Surgical Oncology Group II[37]	1986	3150	180	181	—	—	50	50 (APR)
Mainz[34]	1977	3450	19	28	42	7†	—	—
European Organisation for Research on Treatment of Cancer[36]	1988	3450	175	166	30	15	59	69
					$P=0.003$†		$P=0.08$	

RT, preoperative radiation therapy, APR, abdominoperineal resection, * B Shank (unpublished data); † statistically significant difference

adjuvant treatment, they can provide valuable background information regarding radiation dose, sequencing and field size Our end-results discussion will be restricted to the relatively few studies in which the patients were randomized.

Radiation dose considerations

There appears to be a trend indicating improved local control as the preoperative dose of radiation therapy is increased[15]. One recent preoperative radiotherapy study[16] examined local control rates with varying doses of radiation. The local control rate at 4000 cGy was 67 per cent, increasing to 91 per cent at 5000 cGy. Another study demonstrated a local control rate of 67 per cent with doses between 5000 and 5499 cGy, increasing to 89 per cent with doses greater than 6000 cGy[17]. It seems apparent that doses of at least 5000 cGy are needed to control microscopic disease if the fraction size is 180–200 cGy per day. Data from randomized trials that have used doses less than 3500 cGy have shown benefit only if the fraction size is 230–500 cGy per day[18].

Sequencing considerations

The integration of radiation therapy and surgery can involve preoperative or postoperative irradiation, or a combination of the two. Preoperative radiation therapy minimizes the risks of tumour cell implantation during surgery and may be most effective against the well-oxygenated cancer cells at the periphery of the tumour mass. These benefits are balanced by the problems in case selection (under- or over-treatment) and by the potentially increased surgical complication rates. Postoperative radiation therapy allows careful case selection based on operative findings and pathological staging. However, residual cancer cells may be hypoxic and less radiosensitive, and the risk of small bowel damage is greater.

The so-called 'sandwich' radiotherapy technique involves preoperative radiation therapy, usually with relatively small doses (500–2000 cGy), followed by postoperative radiation to a higher total dose for high-risk cases. Enthusiasts for this method believe that the advantages of both preoperative and postoperative radiotherapy are combined.

Field size

With the radiation doses that must be used to control microscopic disease the major organ at risk for injury is the small bowel If a large portion of the small bowel receives more than 5000 cGy, there is an increased risk of complications such as obstruction, perforation or fistula formation. The volume of the treatment field is an important determinant of the risk of small bowel damage. Preoperative field sizes can be smaller than those considered adequate in the postoperative setting. The short-term effects are related to the volume of small bowel treated while the long-term effects are related to the volume of small bowel receiving a dose greater than 4500 cGy and a history of prior pelvic surgery[19].

Techniques to minimize small bowel toxicity

In addition to the field volume, small bowel complications also relate to the radiation energy, fraction size, total dose, technique and overall treatment duration. The risk of complications may be influenced by other patient-related factors such as age, body habitus, sex, atherosclerosis, hypertension or diabetes. Many techniques[20–30] have been developed to minimize toxicity. These include excluding the small bowel from the pelvis by peritoneal repair, retroversion of the uterus, omental flaps[21] and insertion of absorbable mesh[22] or porcine dermis[23]. As in surgery, radiation technique influences complications. Considerations include using small bowel contrast during treatment planning, multiple fields, prone treatment, bladder distension and abdominal compression. Recent approaches have studied diet regulation[26–28] and the use of radioprotective agents[29,30].

Results in randomized trials with adjuvant radiation therapy

Preoperative radiation therapy

A summary of the major randomized preoperative studies[18,31–37] is shown in *Table 1*. Relatively low doses varying from 500 to 3450 cGy were used with various fraction sizes and treatment durations. Low dose levels with small fraction size

Table 2 *Randomized postoperative radiation therapy studies*

Study	Year	Dose (cGy)	No RT	RT	Dukes' classification	Local recurrence rate (%)		5-year survival rate (%)	
						No RT	RT	No RT	RT
Gastrointestinal Tumor Study Group[40,41]	1985, 1986	4000–4800	58	50	B_2, C	24	20	43	52
National Surgical Adjuvant Breast and Bowel Project[42]	1988	4600–4700 ± Perineal boost	184	184	B_2, C	25	16	43	41 (Overall)
								30	34 (DFS)
Denmark[43]	1986	5000 (Split course)	250	244	B	12	12	67	82 (DFS)
					C	25	21		
		If more than 4500 cGy delivered			B		9		
					C		16		

RT, postoperative radiation therapy; DFS, disease-free survival

appear ineffective. 'Suboptimal' dose levels with a large fraction size appear to reduce local failure[18].

The most impressive results are those reported by the European Organisation for Research on Treatment of Cancer (EORTC)[36]. In this study 341 patients were randomized to preoperative radiation therapy using 15 fractions of 230 cGy per day over a 19-day span *versus* surgery alone. At 5 years, the actuarial local disease-free survival rate was 85 per cent for the preoperative radiotherapy group compared with 70 per cent for the surgery alone group. The Stockholm Rectal Cancer Study Group analysed 545 patients who had potentially curative surgery Half had received 2500 cGy over 5–7 days preoperatively. The pelvic recurrence rate was halved by irradiation ($P<0.01$).

In the studies with doses below 3000 cGy, there has been no reported improvement in overall survival An exception is the Veterans Administration Surgical Oncology Group (VASOG) I study[32] in which patients who had preoperative irradiation (2500 cGy) and abdominoperineal resection had a 41 per cent 5-year survival rate compared with 28 per cent for those having surgery only. Of the studies using doses higher than 3000 cGy, the EORTC[36] reported a difference in disease-free survival between the two groups. With a median follow-up of more than 4 years, the overall actuarial 5-year survival rate in the radiated patients was 10 per cent greater than the surgery alone group, but this reaches only the $P=0.08$ level of significance.

Two studies from the USSR[38,39] have shown statistically significant increases in survival, but it is not clear whether they were properly randomized.

In terms of complications with low-dose radiotherapy, the most complete observations were made in the UK Medical Research Council study[35]. In this study, the complications were essentially identical between the two radiotherapy groups and the surgery alone group with the exception that there was a significant decrease in anastomotic leak rate in the radiotherapy groups compared with the surgery alone group. No increase was observed in the risk of long-term complications. In the VASOG II[37] and the EORTC[36] studies most complications were similar in treated and control groups except for an increase in perineal wound infections in the radiotherapy groups

Postoperative radiation therapy

There have been three major randomized studies that include a 'surgery only' arm compared with postoperative radiation therapy. These reports, summarized in *Table 2*, were from the Gastrointestinal Tumor Study Group (GITSG)[40,41], the National Surgical Adjuvant Breast and Bowel Project (NSABP)[42] and a consortium of institutions in Denmark[43]. Statistically significant improvements in local control have not been shown. However, in the two studies that have been fully reported[40,42] protocol violations were frequent. In the largest trial (NSABP), the local recurrence rate was reduced from 25 to 16 per cent with radiation therapy ($P=0.06$).

No survival difference has been seen at 5 years in any of these studies, although the study from Denmark is not yet mature. In the GITSG trial there was a trend towards an increased survival rate in the radiation therapy group (52 per cent) *versus* the surgery only group (45 per cent). It is of interest that only after 5 years is there a significant survival difference in the combined chemotherapy–radiation arm in this trial This suggests that in any of these studies a decrease in local recurrence rate may not translate into a survival advantage for many years

Adjuvant systemic single agent chemotherapy

Multiple randomized trials of adjuvant 5-fluorouracil (5-FU) in colorectal cancer patients have not demonstrated any consistent benefit However, three groups[44–46] reported rectal patients separately, with an improvement in survival in two studies. The negative trial[44] used an unsatisfactory regimen of oral 5-FU administration and randomized 156 patients, 55 of whom had rectal cancer. All patients received intraluminal 5-FU. The treated group subsequently received two doses of intravenous 5-FU (10 mg/kg), then five 18-day cycles of oral 5-FU The results of this trial were negative, but the number of rectal cancer patients analysed was too small to detect a modest improvement in survival.

Higgins and colleagues in the Veterans Administration Surgical Adjuvant Group entered colorectal cancer patients in several adjuvant chemotherapy studies including an assessment of prolonged intermittent treatment with 5-FU[45] Two hundred and fifty-seven patients with either T2,N1–2, T3–4,N0–2 rectal cancer or any local stage with evidence of vascular invasion were randomized to surgery alone or to surgery and adjuvant 5-FU. The 5-FU was given on five successive days as an intravenous bolus (12 mg/kg), repeated every 6–8 weeks for 18 months. There was a small survival advantage for the treated patients, which in those requiring an abdominoperineal resection reached an almost 10 per cent survival rate advantage at 5 years (43·3 per cent for treated patients *versus* 33·7 per cent for controls)

Grage and members of the Central Oncology Group entered 394 colorectal cancer patients in a study of intensive adjuvant 5-FU[46] The treatment programme involved intensive intravenous 5-FU pushed to toxicity for 12 days, followed by weekly 5-FU (12 mg/kg) for 1 year. Of the fully evaluable patients who had a potentially curative resection, 64 rectal cancer patients were analysed separately The overall incremental survival rate in the 5-FU group was 20 per cent after a follow-up of 29 months ($P=0.005$).

Table 3. *Recently completed rectal cancer postoperative adjuvant trials*

Study	Protocol	Dukes' classification	Patient accrual	Treatment	No of evaluable patients
Gastrointestinal Tumor Study Group[40,41]	7175	B_2, C	227	Control	58
				MF	48
				Pelvic RT	50
				RT+F then MF	46
North Central Cancer Treatment Group[48]	79-4751	B_2, C	200	Pelvic RT	100
				MF/RT+F/MF	100
National Surgical Adjuvant Breast and Bowel Project[42]	R-01	B, C	551	Control	173
				Pelvic RT	177
				MOF	178

All patients underwent a complete surgical resection M, methyl CCNU; O, vincristine, F, 5-fluorouracil; RT, radiation therapy

Adjuvant combination chemotherapy and combined chemotherapy: radiation therapy

In order to minimize local and distant disease recurrence after primary resection, various combinations of surgery, pelvic radiation therapy and systemic chemotherapy have been evaluated[47]. Three recently completed randomized studies[40–42,48] are of particular relevance. As summarized in *Table 3*, these studies evaluated postoperative pelvic radiotherapy and combination chemotherapy together. Two had surgery only control groups[40–42] and two had combined radiation and chemotherapy groups[40,48].

The GITSG trial[40,41] was initiated in 1975 and allocated completely resected Dukes' B_2 and C patients to one of four groups: surgery alone; methyl CCNU (130 mg/m^2 on day 1) and 5-FU (325 mg/m^2 on days 1–5, then 375 mg/m^2 on days 36–40), the cycle being repeated every 10 weeks for 18 months; 4400–4800 cGy to the pelvis; 4000–4400 cGy plus 5-FU/methyl CCNU as above. At a median follow-up time of 80 months the control population had a 55 per cent recurrence rate compared with a 33 per cent rate for the combination radiotherapy–chemotherapy group ($P<0.009$). In the control group 14 of 32 patients had a local recurrence compared with five of 46 patients in the combination therapy group. A subsequent analysis at 94 months' median follow-up demonstrated an even larger margin of benefit for the combination therapy group[41]. In addition to a disease-free survival advantage, the combination radiation–chemotherapy group demonstrated a statistically significant overall survival benefit ($P=0.005$). There was an approximately 20 per cent increase in survival rate at 6 years for the 96 patients at risk.

The second major rectal cancer adjuvant trial was initiated by the North Central Cancer Treatment Group (NCCTG) in 1979[48]. A total of 200 Dukes' B_2 and C rectal cancer patients were randomly assigned to either postoperative radiotherapy alone (4500 cGy with a 500-cGy boost) or to an integrated programme of methyl CCNU (130 mg/m^2 on day 1) plus 5-FU (350 mg/m^2 on days 1–5 and 400 mg/m^2 on days 36–40), radiation beginning on day 64, followed by one additional cycle of methyl CCNU plus 5-FU. The radiation dose was 4500–5000 cGy. At a median follow-up time of 29 months, there were 38 recurrences in the radiotherapy group compared with only 23 in those receiving the combination. There was a doubling of the disease-free survival rate in patients undergoing sphincter-saving surgery followed by the combination treatment compared with postoperative radiotherapy alone. The local failure rate in the combination treatment group was 11 per cent *versus* 20 per cent with irradiation only. The overall disease-free survival rate was superior with combined treatment ($P=0.001$) The time interval to tumour recurrence was statistically superior for the combination therapy group ($P=0.025$). Overall survival differences could not be reported since the data were not sufficiently mature.

The largest study was performed by the NSABP[42]. A total of 528 Dukes' B_2 and C patients were randomized to receive: postoperative observation; postoperative pelvic radiotherapy, 4700 cGy with a boost to a maximum of 5300 cGy; or 18 months of chemotherapy with methyl CCNU, vincristine and fluorouracil (MOF). A combination chemotherapy–radiation arm was not included in the study design. With a 54-month mean follow-up time, there was a statistically significant disease-free survival advantage for MOF chemotherapy ($P=0.05$) and an overall survival improvement only for selected MOF-patient subsets, particularly men ($P<0.02$) and most notably men aged less than 65 years ($P<0.001$) Patients receiving only radiotherapy had no statistically demonstrable improvement in overall or relapse-free survival. In this group, however, there was a reduction in locoregional recurrence rate attributable to radiotherapy from 25 to 16 per cent, although this was not found to be statistically significant ($P=0.06$). Despite the 80 weeks of MOF chemotherapy, leukaemia has not yet been observed[49].

In contrast to the above studies[40,44,48], the EORTC study was unable to show a benefit with combined treatment[50]. This study of preoperative adjuvant therapies compared irradiation with 3400 cGy in 230-cGy fractions to the same radiation dose combined with only 4 days of intravenous bolus 5-FU (375 mg/m^2) during the first 4 days of radiotherapy. In the 247 patients followed, overall survival was better with radiotherapy alone. Although the incidence of liver metastases was reduced in the combined radiation–chemotherapy group, this was not statistically significant ($P=0.07$).

While adjuvant combined modality therapy may yield improved survival, there is the potential for considerable treatment-related morbidity. In the initial GITSG report[40] the acute toxicities encountered were considered generally acceptable, with 25 per cent of those receiving both radiotherapy and chemotherapy having a white cell count lower than 2000/mm^3. However, the morbidity related to treatment in the GITSG trial[41] was in fact quite extensive and was the subject of a separate report[51]. Severe or life-threatening acute toxicities occurred in 18 per cent of patients in the radiotherapy arm and in 61 per cent of those in the combined radiotherapy–chemotherapy arm. Three late deaths occurred. two from radiation enteritis in the combined treatment group and one from non-lymphocytic leukaemia in a patient receiving chemotherapy alone. There is good evidence to show that radiation-induced morbidity can be minimized by using some of the techniques previously mentioned Many of these precautions were not observed in this trial.

Specific unresolved issues and current studies

Radiation therapy and/or surgery sequencing issues

In relation to radiation therapy sequencing techniques, two major studies are currently active. In Sweden a multicentre trial was launched in late 1980 to compare randomly pre-operative and postoperative radiotherapy for resectable rectal cancer. The preoperative treatment consists of five fractions of 510 cGy to a total tumour dose of 2550 cGy delivered in 5–7 days. In the postoperative treatment group, only patients with Astler–Coller stages B2, C1 and C2 are irradiated. After the first 4 years of the trial, when 360 patients had been randomized, an interim report was prepared[52]. It is of note that in the preoperative treatment group the radiation was well tolerated, the only significant problems encountered being an increase in perineal wound sepsis and an increase in the mean duration of hospital stay. For the postoperative group considerable difficulties were encountered in completing the programme of irradiation. A total of 8 per cent of the preoperatively treated group had disease limited to the mucosa and submucosa compared with 6 per cent of the remainder Using life table analysis local recurrence rates were 10 and 12 per cent respectively for the preoperative and postoperative treatment groups

The Radiation Therapy Oncology Group (RTOG) together with the Eastern Co-operative Oncology Group (ECOG) are conducting a phase III randomized trial of 'sandwich' radiotherapy *versus* postoperative radiotherapy alone for Dukes' A, B and C rectal cancer. Patients are randomly allocated to receive preoperative radiation (500 cGy) or not. After surgery all patients with Dukes' B_2 or C disease receive 4500 cGy to the pelvis.

Prognostic issues

Selection of patients for preoperative irradiation remains uncertain. Clinical, radiological and biological studies may be able to define the high-risk group most likely to benefit from preoperative irradiation Intraluminal rectal ultrasonography has proved to be an accurate means of defining the extent of transmural invasion. It is somewhat less reliable in the accurate diagnosis of perirectal nodal metastases[53]. Combined with clinical staging[54], it may allow definition of those patients most suitable for preoperative radiation therapy.

DNA distribution was first recognized as a possible prognostic factor for rectal cancer in 1982[55]. Indeed, striking differences were noted in outcome when patients with predominantly diploid tumours were compared with those with the more aggressive non-diploid lesions. DNA ploidy has not been universally found to be an independent prognostic indicator, especially when examined in a multivariate fashion It has however been shown to be a prognostic discriminant in univariate analysis, and as it can be assessed on preoperative biopsy material it may yet prove to be worthy of consideration[56,57].

The extent to which transforming cellular oncogene expression is related to the clinical behaviour of tumours continues to be of great interest[58] It has been suggested that the expression of *ras* family oncogenes may be related to disease progression; for example, *c-myc* over-expression was associated with a much greater chance of early recurrence of cervical cancer[59]. In a small group of patients *ras* gene activation has been associated with the depth of invasion of colorectal cancer[60] while others have failed to demonstrate any relationship with clinical outcome[61].

Laparoscopy is a convenient technique to detect both macroscopic peritoneal metastases and deposits visible on the surface of the liver. For gastric cancer it has been shown to be an accurate method of detecting previously undetected liver metastases[62,63] although neither of the studies reporting its value made use of preoperative computed tomographic scanning. The extent to which laparoscopy can add to the available methods for detecting previously occult metastases in rectal cancer remains unexplored

The use of monoclonal antibodies in radioimmunodetection of regional nodal metastases and distant disease remains at an early investigational stage[64].

Radiation treatment issues

Crucial to the efficacy and toxicity of radiation therapy is both fraction and treatment portal size. Preoperative irradiation to 5040 cGy in fractions of 180 cGy per day needs to be compared with doses of 2500–3500 cGy in fraction sizes as great as 550 cGy. In such a study, local control and both early and late complication rates must be compared Advances in computerized three-dimensional treatment planning may dramatically reduce radiation-induced toxicity.

Chemotherapy issues

Issues relating to systemic chemotherapy agents are being investigated in two ongoing large co-operative randomized trials in the USA (*Table 4*). The NCCTG study 86-4751 utilizes a 2 × 2 factorial statistical design and attempts to quantify the relative benfits of continuous infusion *versus* bolus 5-FU as well as the necessity of including methyl CCNU in the chemotherapy regimen All patients receive pelvic radiotherapy and concomitant 5-FU in the sequence chemotherapy–radiation–chemotherapy. Half the patients receive methyl CCNU plus 5-FU chemotherapy as in the previous NCCTG trial; the other half receive 5-FU, 500 mg/m^2 on days 1–5 and on days 36–40 before radiation, and 450 mg/m^2 on days 1–5 and on days 36–40 1 month after radiation. During radiotherapy, patients receive either standard 5-FU, 500 mg/m^2 on days 1–3 and on days 36–39 as an intravenous bolus, or a continuous intravenous infusion at 225 mg/m^2 daily for 5 weeks The planned pelvic radiotherapy dose consists of 4500 cGy with a boost to a total of 5400–5900 cGy.

In male patients, the recently activated NSABP R-02 study compares their standard MOF chemotherapy with a 5-FU/leucovorin programme and is complementary to their C-03 study for colon cancer patients.

The integration of portal and systemic venous chemotherapy must be considered if benefit is confirmed in colon cancer. The rationale for adjuvant perioperative intraportal chemotherapy is based on the observation that, at the time of surgery, tumour cells embolize into the portal venous system and reach the liver[65,66]. Fisher and Turnbull[67] demonstrated tumour cells in the portal circulation in 32 per cent of patients at the time of colonic carcinoma resection. Moreover, there is considerable clinical and autopsy evidence that the liver may be the most frequent, and sometimes the only, site of metastasis[65,66]. Although established metastases are supplied primarily by the hepatic artery, micrometastases are likely to be dependent on the portal venous blood supply[68]

In 1975 Taylor *et al.*[69] began a randomized study comparing intraportal 5-FU (700 mg/m^2 per day) with heparin for patients with Dukes' A, B and C colorectal cancer. A continuous 7-day infusion was started in the immediate postoperative period.

Table 4 *Currently active North American co-operative group rectal cancer postoperative adjuvant trials*

Study	Projected accrual	Treatment
North Central Cancer Treatment Group (86-4751)	450	MF, RT + F infusion, MF MF, RT + F bolus, MF F, RT + F infusion, F F, RT + F bolus, F
National Surgical Adjuvant Breast and Bowel Project (R-02)	800	Men MOF MOF + RT F + leucovorin F + leucovorin + RT Women F + leucovorin F + leucovorin + RT
National Cancer Institute, Canada (CO-4)	425	RT F + leucovorin, RT, F + leucovorin

All patients undergo complete surgical resection; pathological stage T3N0M0 or TXN1-2M0 (modified Astler–Coller B_2/C). M, methyl CCNU; F, 5-fluorouracil, O, vincristine, RT, radiation therapy

Two hundred and twelve patients were studied and, by 1985, 80 deaths had occurred. The median follow-up was greater than 50 months. The Dukes' B colon cancer group appeared to have a substantial survival benefit ($P = 0.002$) with intraportal venous 5-FU. This preliminary study stimulated several randomized trials of generally similar design. In Australia and New Zealand a trial evaluated 372 colon cancer patients randomly allocated to observation alone or to immediate postoperative chemotherapy, 5-FU 600 mg/m^2 daily for 7 days given either intravenously or intraportally. Compared with both of the other groups, portal vein 5-FU resulted in highly significantly superior disease-free and overall survival rates[70]. These data are not fully mature and require further follow-up in order to determine the magnitude of the survival benefit. A second study of similar design was conducted by the Swiss Group for Clinical Cancer Research (SAKK)[71]. From 1981 to 1986, 378 evaluable Dukes' A, B or C patients who had complete resection of colorectal cancer were allocated either to a control group or to a chemotherapy group receiving immediate postoperative intraportal 5-FU (500 mg/m^2 daily) with 5000 units heparin given by continuous infusion for 7 days. On the first day of therapy, a 10 mg/m^2 bolus of mitomycin C was also administered. After a median follow-up of 24 months, recurrences were detected in 43 of 187 (23 per cent) control patients compared with 34 of 191 (18 per cent) infused patients ($P < 0.05$). Too few deaths have occurred to permit a significant difference in survival to be detectable, and a longer follow-up period is required before conclusions can be definitely drawn.

There are two active phase III trials evaluating colon cancer patients in the USA. Of special importance is the NSABP C-02 study as, with 1334 patients, it will be the largest single portal vein trial. It is anticipated that both studies will complete accrual in 1988 and that preliminary survival data will be available 1–3 years thereafter

Systemic chemotherapy–radiation therapy interaction

The recently activated NSABP R-02 study will attempt to confirm the GITSG and NCCTG results which indicated that both local control and overall disease-free survival were maximized by combining chemotherapy with pelvic irradiation. Male patients will be randomized to methyl CCNU/vincristine/5-FU (MOF) *versus* 5-FU/leucovorin. Half of the patients will receive radiotherapy in conjunction with chemotherapy. Because of the suggestion that the benefits of MOF were limited to men[42], women will receive 5-FU/leucovorin with or without radiation while men will be randomized amongst the four therapy options. The National Cancer Institute, Canada, NCIC CO-4, protocol will evaluate an integrated programme of 5-FU/leucovorin chemotherapy and X-ray therapy in comparison to postoperative pelvic radiotherapy alone.

The integration of postoperative chemotherapy and irradiation may lead to improved survival, but with excessive toxicity[40]. Comparisons of the therapeutic ratio obtainable with surgery–X-ray therapy–chemotherapy sequencing (NSABP) must be compared with the surgery–chemotherapy–X-ray therapy–chemotherapy (NCCTG) approach. The integration of chemotherapy into the preoperative irradiation approaches has yet to be explored Sequential *versus* simultaneous chemotherapy/X-ray therapy approaches must be compared.

Biological response modifiers

An immunotherapy regimen, either alone or in combination with chemotherapy, was used in the adjuvant treatment of colon cancer, with mixed results[72] Adjuvant immunotherapy has not been definitively tested in rectal cancer patients. In a study from Leicester[73], 141 colorectal cancer patients were randomized to receive either surgery alone, surgery plus 5-FU (1·0 g intravenously after operation and repeated on the first two postoperative days then 1·0 g orally every week for the next 6 months), or surgery plus 5-FU with the addition of the non-specific immunostimulant levamisole (150 mg orally on each of the first three postoperative days). With a minimum follow-up of 5 years, the cancer-specific survival rate was 48 per cent for the controls, 56 per cent for the chemotherapy group and 68 per cent for the combination therapy group. A strongly positive trial of adjuvant 5-FU and levamisole has also been reported by the NCCTG[74]. The current Intergroup 0035 study is attempting to confirm these data

Other approaches undergoing trial in colon cancer patients include the use of BCG and autologous tumour cell vaccine (ECOG, EST-5283) and recombinant interleukin 2 (Illinois Cancer Council, ICC-8614).

If the efficacy of any of these approaches in colon cancer is demonstrated, biological response modifiers will have to be integrated into the already complex multimodality rectal cancer regimens.

Current recommendations based on the above data

The randomized studies described indicate that meaningful survival benefits can be achieved with programmes of postoperative adjuvant chemotherapy. Preoperative or postoperative radiation therapy can reduce the risk of developing potentially catastrophic local recurrence. The combination of radiation and chemotherapy may offer the greatest survival advantage[47]. What remains unclear is: the exact choice of chemotherapeutic agents to maximize overall survival and to minimize toxicity; the route of administration and duration of these drugs; the scheduling and dosage of radiation; and the logistics of integration of all three methods of treatment (surgery, radiation therapy and chemotherapy).

While awaiting the complete analysis of the ongoing studies, some form of adjuvant therapy is recommended for most patients with extraperitoneal rectal cancer with transmural penetration and/or positive lymph nodes. The case seems most convincing for patients whose primary tumours invade locally into adjacent structures or where there is gross transmural extension with involved lymph nodes. Whenever possible, participation in a formal clinical trial is to be encouraged However, for those not entering a clinical study, the choice of adjuvant therapy is contingent on many medical, psychological and social factors which must be considered by the patient and physician. For many patients the use of preoperative or postoperative radiation therapy with postoperative 5-FU chemotherapy is a reasonable programme at present.

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Gallbladder carcinoma: role of radiation therapy

S. Houry, M. Schlienger*, M. Huguier, F. Lacaine, F. Penne* and A. Laugier*

*Service de Chirurgie Digestive and *Service de Radiothérapie, Hôpital Universitaire Tenon, Paris*

Correspondence to:
Dr S. Houry, Service de Chirurgie Digestive, Hôpital Tenon, 4 Rue de la Chine 75020 Paris, France

Gallbladder carcinoma continues to be a discouraging disease. Prognosis after resection still remains poor. Radiation therapy has been used in an attempt to improve the prognosis but only a few series of less than ten cases have been reported. Since 1977 we have treated 20 patients with gallbladder carcinoma with postoperative radiotherapy (mean total dose 4200 radiation absorbed dose). In four patients all the tumour was resected with the intent of cure. In 12 patients, the lesion was partially resected and in four patients no resection was performed. Seven patients in whom the tumour was partially resected or not resected also had chemotherapy. Our evaluation was retrospective and we compared our results with historical control groups comparable with respect to surgical procedures and pathological staging. In patients operated on for cure, one patient is alive at 84 months, the others died at 7, 8 and 33 months. In patients in whom the tumour was partially resected the mean survival time was 8·1 months and two patients are still alive 7·0 months after treatment. According to the Nevin classification the mean survival time in stage IV and V patients was respectively 9·2 and 7·2 months. There was no difference in survival between patients treated or not treated with chemotherapy. This experience is the largest published and suggests that radiotherapy may increase survival after no resection or palliative resection of gallbladder carcinoma.

Keywords: Gallbladder carcinoma, radiotherapy

Gallbladder carcinoma is found in 1–2 per cent of patients who undergo surgery on the biliary tract[1]. It is characterized in most clinical reports by late diagnosis, ineffective treatment and poor prognosis. Actual procedures performed on 3000 patients drawn from 87 series included biopsy alone in 34·4 per cent, palliative procedures in 23 per cent, cholecystectomy with or without hepatic resection and/or lymph node dissection in 38·8 per cent, and other procedures in 3·8 per cent of the cases[1]. Two-thirds of cholecystectomies are palliative, and one-third potentially curative[2]. The overall 1-year and 5-year survival rates in 5836 collected cases were 11·8, and 4·1 per cent respectively[1]. In patients who underwent palliative procedures, 5-year survival was achieved in 0·4 per cent[1].

Adjuvant radiotherapy has not been adequately evaluated in these patients, and therefore its value after surgery is unknown. Only a few sporadic, almost anecdotal, reports concerning the use of adjuvant radiotherapy have been reported[2–4]. No specific series presents more than ten cases, and most include carcinoma of the biliary tract with carcinoma of the gallbladder[5,6]. The aim of this report is to assess the role of postoperative radiotherapy in 20 patients operated on for carcinoma of the gallbladder.

Patients and methods

A review of the cases registry at our Division of Radiotherapy revealed 20 patients with gallbladder carcinoma who were treated postoperatively with a complete course of radiotherapy between May 1977 and November 1987. One other patient was excluded from the study because of failure to complete the planned course of radiotherapy. He refused further therapy after receiving only 1400 radiation absorbed dose (rad) of a planned 4500 rad. The remaining 20 patients constitute this series. Seven patients were men and 13 women. They ranged in age from 50 to 74 years (mean age 63·5 years). The presenting symptoms were those of biliary pain or cholecystitis (ten patients), jaundice (nine patients), and an abdominal mass (three patients). Weight loss was noted in four patients and not mentioned in the case histories of the others. Primary gallbladder carcinoma was diagnosed preoperatively in three patients. All 20 patients were operated on and were found to have single or multiple gallstones associated with the carcinoma. Three patients operated on for cholecystitis were found to have carcinoma of the gallbladder only at pathological examination.

The operative procedure was exploratory laparotomy with biopsy alone in two patients, and with palliative biliary diversion in two other patients (Roux-en-Y hepaticojejunostomy). Cholecystectomy was performed in 16 patients (partially in three of them). Additional lymph node dissection was performed in two cases, liver resection of the gallbladder wedge in two cases, and partial liver resection in two cases (one metastasectomy, and one bisegmentectomy for direct liver involvement). Other operative procedures after partial or total resection of the tumour consisted of colectomy (one case) and biliary drainage (three Roux-en-Y hepaticojejunostomy and one placement of a drainage tube into the common bile duct).

On histopathological examination all tumours were adenocarcinomas, well differentiated in 16 cases and poorly differentiated or undifferentiated in four cases. According to the pathological staging system reported by Nevin *et al.*[7], no patient was in stage I (intramucosal) or II (invasion of muscularis mucosa), two patients were in stage III (invasion of all layers of gallbladder wall), four in stage IV (cystic node involvement) and 14 in stage V (distant spread: liver or adjacent organs).

The time between initial surgery and radiotherapy was usually 3·5 weeks. Total doses given ranged from 3200 to 5500 rad (mean 4200 rad). The usual weekly dose was 1000 rad in four sessions. Patients were treated with 18×10^6 eV X-rays from a 20×10^6 eV linear accelerator (Saturne 20 CGR MeV, Buc, France). Parallel opposed anterior and posterior fields to the right upper quadrant were used. Clips placed at surgery were often used to determine the treatment fields. *Table 1* lists pertinent data on the 20 patients.

Seven patients were also given chemotherapy, the agents used and the number of sessions are listed in *Table 2*.

Results

No adverse effect or complication was noted after radiotherapy. In all jaundiced patients who had palliative biliary drainage, jaundice and pruritus disappeared after surgery and before radiotherapy. The jaundiced patients who had laparotomy and biopsy without a drainage procedure remained jaundiced after radiotherapy.

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Table 1 *Survival time of 20 gallbladder carcinomas according to pathological staging, surgical procedure and adjunctive therapy*

Patient number	Nevin staging	Surgical procedures	Radiotherapy (dose)	Survival (months)
Operated on with intent of cure				
1†	III	Cholecystectomy	4500	84*
2†	V	Cholecystectomy, resection biliary tract, hilar Roux-en-Y anastomosis, liver wedge resection	4500	7
3	III	Cholecystectomy	5500	33
4†	IV	Cholecystectomy	5000	8
Palliative surgery				
5	IV	Cholecystectomy	5000	13
6	V	Partial cholecystectomy, Roux-en-Y anastomosis	5000	11
7	V	Cholecystectomy, liver bisegmentectomy	4000	4
8	V	Cholecystectomy, omentectomy	3200	7
9	V	Cholecystectomy, biliary tube placement	5000	4
10	V	Cholecystectomy, lymph node dissection	5000	9
11	V	Cholecystectomy, liver metastasectomy	4000	12
12	IV	Cholecystectomy, Roux-en-Y anastomosis	5000	6·5
13	V	Cholecystectomy	4500	8
14	IV	Partial cholecystectomy	3200	7*
15	V	Partial cholecystectomy	3200	7*
16	V	Cholecystectomy, lymph node dissection, liver wedge resection, colectomy	4200	7
17	V	No resection performed, Roux-en-Y anastomosis	3200	6·5
18	V	No resection performed	3200	6
19	V	No resection performed, Roux-en-Y anastomosis	4500	10
20	V	No resection performed	4000	2·5

* Patient still alive; † patients in whom the diagnosis was a histological finding, for patient 2, staging was established after reintervention for biliary tract resection

Table 2 *Chemotherapy programme, and survival time in seven of 20 gallbladder carcinomas*

Patient number	Cytostatic agents	Number of sessions	Survival in months
8	5-Fluorouracil, doxorubicin	4	
	Mitomycin, cyclophosphamide	2	7
10	5-Fluorouracil, doxorubicin, vinblastine, cyclophosphamide	5	9
11	5-Fluorouracil, doxorubicin, mitomycin	6	12
13	5-Fluorouracil, cisplatin	3	8
15	5-Fluorouracil, cisplatin	4	7*
17	Bleomycin	1	6·5
18	5-Fluorouracil	2	6

* Patient still alive

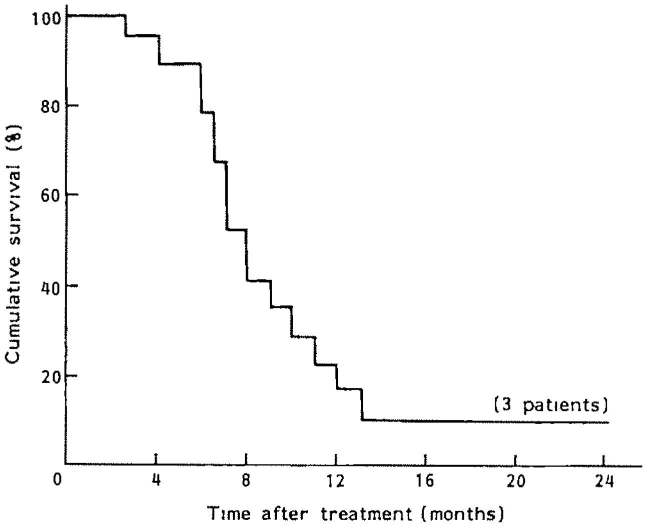

Figure 1 *Survival curve for 20 carcinomas of the gallbladder treated with postoperative radiotherapy*

The cumulative survival curve (Kaplan–Meier) for all patients is shown in *Figure 1* The median survival of the entire group was 8 months Three patients are alive, two at 7 months after partial cholecystectomy, and one at 84 months after cholecystectomy The mean survival time for the other patients was 9 months. According to Nevin's staging, the patient alive at 84 months was Nevin III, and the two patients alive at 7 months were staged Nevin IV and Nevin V respectively. The mean survival time was 9·2 months for patients staged Nevin IV, and 7·2 months for patients staged Nevin V

According to the operative procedures, two groups of patients were collected. A group of four patients in whom all of the tumour was apparently resected constituted the group operated on with intent of cure. Two tumours were staged Nevin III, one Nevin IV, and one Nevin V None of those patients received chemotherapy but all received 4500–5500 rad postoperatively (*Table 1*). In this group, one patient (Nevin III) is alive with no sign of recurrent disease at 84 months after cholecystectomy. The three others died, one 7 months after a reoperation for wedge liver and biliary tract resection (he had undergone prior cholecystectomy), while two died 8 and 33 months after cholecystectomy.

A group of 16 patients in whom the tumour was not resected or partially resected constituted the group having palliative surgery; the median survival time was 7 months but two patients were still alive at 7 months. These two patients had partial cholecystectomy, and received 3200 rad postoperatively, one of them underwent four sessions of chemotherapy. The mean survival time for the remaining patients was 7·6 months. In 12 patients from the group in which the lesions were partially resected, mean survival time was 8 1 months and median survival time was 7·5 months In four patients from the group in which laparotomy with no resection of the tumour was performed (two having palliative biliary drainage), mean and median survival times were both 6·2 months.

After palliative surgery, one patient treated with chemotherapy and one without chemotherapy are still alive. Mean survival of the remaining patients irradiated and treated with chemotherapy was 8 months, and in those irradiated without chemotherapy it was 7·2 months. The difference is not statistically significant. Survival of all patients according to pathological staging, surgical procedure and adjuvant therapy is listed in *Table 1*.

Discussion

Published reports concerning the role of radiotherapy in gallbladder carcinoma are disappointing for many reasons: (1) results are conflicting[2,5,6]; (2) whatever the results obtained, no series has exceeded ten cases and all include heterogeneous lesions[5,6,8]; (3) in almost all series the radiation dose is not specified[2,3]; (4) all specific reports of radiotherapy have included carcinoma of the biliary tract with gallbladder carcinoma[5,6,8]; and (5) the results have not been related clearly to consistent staging of the disease. This lack of evaluable data has led us to report our experience Even in large institutions there are only a few suitable cases per year and a randomized clinical trial cannot be carried out without multicentre collaboration. Thus, our investigation was retrospective and we have made comparisons with results obtained by others We have tried to evaluate the role of adjuvant radiotherapy in homogeneous groups according to pathological extension and operative procedures. Thus, we separated two groups in which the prognosis is quite different, a group operated on 'for cure' with complete resection of the tumour and its extension, and a palliative surgery group with no resection or partial resection of the tumour. If the tumour is believed to be completely resected, in spite of a poor overall 5-year survival of approximately 3 per cent[1], some authors have reported cases of prolonged survival after surgery alone[9]. This possibility and the dearth of published cases where postoperative radiotherapy has been used in these patients prompted us to try to assess the benefit of such adjuvant therapy. In our series only four patients were operated on for cure and irradiated. One is still alive, the three others died. After palliative surgery without radiotherapy, the prognosis seems well established in published series and a comparison could be performed with our own results The mean survival time of patients operated on with any tumour resection is reported to vary between 1·5 and 2 months[1,10]. In our patients irradiated after laparotomy with biopsy alone, the mean survival time was 6·2 months. In the same way, patients in whom the tumour has not been totally resected usually have a survival time of less than 6 months[1,11]. In our series the survival time for these patients seems to be improved by postoperative irradiation. Two patients were still alive 7 months after treatment, and the mean survival time for the remainder was 8 1 months. Nevin *et al* [7] have correlated depth of invasion and histological grade of tumour with survival and the mean survival time was less than 6 months for stage IV and V cases Morrow *et al.*[11] in a series of 112 patients with gallbladder carcinoma operated on reported comparable survival patterns, i.e. 5 months for 13 patients with stage IV and 3 months for 88 patients with stage V. Compared with this series, our patients irradiated after surgery had a longer survival time, respectively 9·2 and 7·2 months.

Some authors have supported the view that radiotherapy is at least of benefit in palliation. Kopelson *et al* [5] reported a 92 per cent success rate with palliation for pain and pruritus However the number of patients discussed was too small and most also had palliative surgery procedures. In our cases the palliation effect of radiotherapy could not be evaluated because all but one of the jaundiced patients had surgical biliary drainage. The jaundiced patient who underwent only a laparotomy and biopsy remained jaundiced after radiotherapy, in spite of a reduction of tumour mass.

We encountered no adverse effects or complications after the dose of radiotherapy used. Nevertheless in order to overcome the so-called 'radioresistance' of gallbladder carcinoma, and to avoid damage by external radiotherapy caused by the increased dose in the irradiation fields, Todoroki *et al.*[8] attempted to use intraoperative radiotherapy for advanced unresectable carcinoma of the biliary tract. A single dose of 2500–3000 rad was delivered after non-curative resection in five patients[8] One was alive after 5 months while the mean survival time for the others was 11·8 months. However in this series half of the patients had a papillary adenocarcinoma, a histological finding which is usually believed to carry better prognosis[11,12].

The only randomized study of chemotherapy was published by the Eastern Cooperative Oncology Group who used such chemotherapy for patients with inoperable gallbladder cancer without showing a significant survival difference between the three chemotherapy regimens evaluated[13] The number of patients treated by radiotherapy and chemotherapy is too small to evaluate the benefit of this association[14].

We conclude that after surgery with the intent of curing gallbladder cancer, the prognosis still remains poor and future study of the use of radiotherapy will be needed to assess the benefit of this adjuvant therapy. In contrast, after palliative surgery, our experience suggests that adjuvant radiotherapy may be associated with increased survival.

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Long-term follow-up after choledochojejunostomy for bile duct stones with complex clearance of the bile duct

D. J. Gouma, J. Konsten, P. B. Soeters, M. Von Meyenfeldt and H. Obertop

Department of Surgery, University Hospital Maastricht, 6201 BX Maastricht, The Netherlands

Correspondence to:
Dr D. J. Gouma

In this retrospective study, the long-term follow-up of patients undergoing choledochojejunostomy (Roux-en-Y) for bile duct stones with complex clearance of the bile duct is evaluated. Bile duct exploration and subsequent choledochojejunostomy (Roux-en-Y) was performed in 43 patients (median age 67 years) in the period 1976–82. There was no mortality and only one patient had a major complication. Twenty patients died during follow-up (median follow-up period 5 years); the median follow-up period for the remaining 23 patients was 8 years. Good long-term results were found in 98 per cent of cases. No signs or symptoms could be related to bile duct obstruction or to cholangitis. Nearly all liver function tests and serum bilirubin levels were normal in the 21 patients who were tested. We conclude that patients with bile duct stones with complex clearance of the bile duct can be safely treated by means of a choledochoenterostomy (in this study a choledochojejunostomy Roux-en-Y).

Keywords: Bile duct stones, choledochojejunostomy, sphincterotomy, biliary drainage

The management of patients with common bile duct stones has changed during the last 10 years after wide acceptance of endoscopic sphincterotomy[1]. Initially this procedure was used only for retained stones[2,3], for high risk patients, and for patients with acute cholangitis[4]. Some authors consider that endoscopic sphincterotomy is the treatment of choice for all patients with common bile duct stones, regardless of the presence of the gallbladder[5–7], believing that the results are more favourable than those for surgery[7].

Nevertheless most patients with cholelithiasis and bile duct stones are still treated surgically by means of cholecystectomy and common bile duct exploration. In 9–12 per cent of these patients bile duct stones are associated with complex clearance of the common duct, indicating that recurrent or retained stones can be expected[8,9]. In these patients internal drainage of the common bile duct can be performed by means of a sphincterotomy or sphincteroplasty, choledochoduodenostomy or choledochojejunostomy[8–10].

With the wide availability of endoscopic sphincterotomy, it has been suggested recently by some endoscopists that 'only simple cholecystectomy should be performed and surgeons should stop worrying about whether stones remain in the bile duct because endoscopic sphincterotomy can simply remove them later'[11]. When drainage is indicated, such endoscopists consider that endoscopic sphincterotomy should be preferred to operative internal drainage because this procedure has been reported to be associated with a lower morbidity and mortality[7,11]. As Johnson and Hosking have described, this approach is leading to the philosophy that 'any procedure is justified if it avoids an operation'[1].

Long-term follow-up data are now available in patients who have undergone endoscopic sphincterotomy, but detailed data drawn from series with follow-up periods of 5 years and a high percentage of follow-up (>90 per cent) are limited. The superiority of the endoscopic approach over surgical choledochoenterostomy, especially in the context of long-term follow-up, has yet to be proved.

Before the availability of endoscopic sphincterotomy, choledochojejunostomy was performed routinely in our hospital in all patients with bile duct stones where complex clearance of the bile duct was thought to justify internal biliary drainage. The present retrospective study evaluates morbidity and mortality of choledochojejunostomy, especially the long-term results.

Patients and methods

In the period 1976–82, 43 patients (21 men and 22 women) drawn from a total of 1380 patients operated on for biliary stones (1016 patients undergoing simple cholecystectomy, 323 patients having cholecystectomy and common bile duct exploration, and 41 patients with only common bile duct exploration) had complex bile duct stones found during common duct exploration (see below); all 43 patients underwent a choledochojejunostomy using a Roux-en-Y loop 60 cm long. Patients operated on after 1982 were excluded from the study to ensure a minimal follow-up period of 5 years.

Patients in whom choledochojejunostomy was performed for other benign conditions were excluded. Choledochojejunostomy was preferred to choledochoduodenostomy because the latter procedure was believed to be associated more frequently with cholangitis caused by retention of food debris in the common bile duct

The median age of the 43 patients was 67 years (range 43–87 years) and 21 patients (49 per cent) were over 70 years of age Previous biliary tract surgery had been performed in 12 patients (simple cholecystectomy in six, cholecystectomy with common duct exploration in five, and cholecystectomy and transduodenal sphincterotomy in one patient) Gastric resection for peptic ulcer had been performed previously in six patients. The preoperative findings are summarized in *Table 1*

At laparotomy all patients underwent common bile duct exploration because of bile duct stones Thirty-seven patients had multiple bile duct stones with or without sludge and gravel, impacted stones, intrahepatic stones and/or cholangitis (*Table 2*). Six patients had a solitary bile duct stone which was impacted in the lower end of the common duct or associated with stenosis or sludge. The indication for internal drainage was based on these findings and on doubt about whether total clearance of the duct could be achieved Stones impacted in the distal bile duct could not always be removed

Data regarding postoperative complications and mortality were drawn from the case records of the patients

Follow-up

The follow-up study was performed in collaboration with the patients' general practitioners, who filled out questionnaires that were sent to

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Table 1 *Preoperative findings in 43 patients with bile duct stones with complex clearance of the bile duct*

	No. of patients
Preoperative findings	
Upper abdominal pain	39 (91)
Fever >38°C	15 (35)
Fever+chills	8 (19)
Jaundice	23 (54)
Risk factors	
Cardiovascular	14 (33)
Pulmonary	2 (5)
Diabetes	8 (19)

Values in parentheses are percentages

Table 2 *Indications for choledochojejunostomy in 43 patients with bile duct stones with complex clearance of the bile duct*

	Multiple stones ($n=37$)	Solitary stone ($n=6$)
Impacted	5	1
Intrahepatic	8	—
Stenosis (distal common bile duct)	4	1
Sludge/gravel	15	2
Severe cholangitis	7	1
Second procedure	10	2

them. Patients who were alive were visited by a nurse who collected blood samples for liver function tests. Data were available from all patients Special attention was paid to signs and symptoms related to cholangitis and/or the so-called 'sump' syndrome (i e. abdominal pain, jaundice and pyrexia) The cause of death of patients who died during the follow-up period was documented and, if available, autopsy findings were recorded. Liver function tests and serum bilirubin concentrations were determined in all but two of the patients alive at the time of the study.

Results

Choledochojejunostomy (Roux-en-Y) was performed in all patients, without technical problems One patient suffered from a major complication (gastric bleeding) postoperatively. A second patient had bile leakage from the Winslow drain that could be managed conservatively Six patients (14 per cent) had a wound infection, two of them leading to dehiscence of the wound. Surgical drainage had to be performed in one patient for an infected haematoma. Four of the six patients with infective complications had suffered from cholangitis before operation. Cardiopulmonary complications and urinary tract infection each developed in six patients (28 per cent) but were managed without difficulty. There was no mortality in this series. The median overall hospital stay and the median postoperative hospital stay were 23 and 13 days respectively

Twenty patients died during follow-up. The median follow-up period for these 20 patients was 5 years (range 2–9 years) Seventeen of the 20 patients had no signs or symptoms before their death that could be related to the previous biliary drainage operation nor was their death related to the operation. Of the remaining three patients, one complained of heartburn and died 9 years after the initial biliary drainage procedure from disseminated breast cancer. At autopsy no ulcer, gastritis or sign of biliary disease was found. The second patient developed a duodenal ulcer 8 years after surgery during treatment with salicylates; liver function tests were normal at that time. She died from colonic cancer 1 year later The third patient developed jaundice, probably due to the use of methyldopa: she died 2 years after surgery and, at autopsy, a patent anastomosis without any sign of obstruction or infection in the biliary tract was found. Thus, of this group of 20 patients, six died from malignancy, three from cerebrovascular disease, two from cardiovascular disease, one from pneumonia, and one from haemolytic anaemia None of the remaining seven patients who died had any sign of biliary disease or sepsis related to the previous drainage procedure.

Twenty-three patients were alive at the time of study The median follow-up period was 8 years (range 5–11 years). No patient had upper abdominal complaints at the time of follow-up and no patient was treated by his general practitioner during the entire period for signs or symptoms related to bile duct stones, stenosis and/or cholangitis. Liver function tests and serum bilirubin concentration in these patients are summarized in *Table 3* The median values were within normal limits although one patient had an isolated increase in alkaline phosphatase concentration. Two patients had an increased γ-glutamyl transferase level, one of whom also had an increased glutamic–pyruvic transaminase concentration. One patient had a borderline bilirubin level.

Discussion

Patients in this study underwent choledochojejunostomy (Roux-en-Y) for bile duct stones with complex clearance of the bile duct before endoscopic sphincterotomy became available, so that elderly patients and those with relatively high operative risk were included Choledochojejunostomy (Roux-en-Y) was performed as a routine when the risk of retained or recurrent stones was present, and no patient was excluded from the study

It still remains difficult to compare the results of this unselected series with those from recent series of patients dealt with by endoscopic sphincterotomy. Endoscopic sphincterotomy is successful in about 90–95 per cent of patients, and in about 85 per cent bile duct clearance is achieved[1,4,6,7,11,12]. Morbidity and mortality rates of this procedure are generally reported to be 2–13 per cent and 0–2 per cent respectively[1,5,7,11]. However, in a selected series of patients unfit for surgery (42 per cent aged over 80 years) Davidson *et al*[13] reported an in-hospital mortality rate of 11·3 per cent. Long-term follow-up results are now available but follow-up is usually relatively short (mean 2–3 years) and incomplete[7,14,15]. Recurrent stones and/or stenoses have been reported in 4–10 per cent of cases[1,2,7,15], although recently a series has been reported in which 21 per cent of patients developed recurrent stones[14]

In the present series internal biliary drainage was achieved in all patients without mortality. Major complications occurred in 2 per cent, and wound infection and other minor complications were reported in 14 and 28 per cent of the patients respectively. Good results after choledochoduodenostomy and choledochojejunostomy have also been reported by others[8,16–18]. Mortality rates of between 0 and 3 per cent have been reported, and the complication rates have varied from 10 to 40 per cent[8,16–18]. Transduodenal sphincterotomy and sphincteroplasty are probably associated with a higher incidence of morbidity (especially pancreatitis) and a mortality rate of up to 4 per cent[16,19]. Mortality rates after simple cholecystectomy and common bile duct exploration are reported to be between 0·5 and 3·0 per cent for patients between 60 and 70 years of age[1,20–22]. Therefore, internal biliary drainage does not seem to increase mortality greatly in most series.

Table 3 *Liver function tests and serum bilirubin concentrations of 21 patients with a choledochojejunostomy who were alive at the time of the follow-up study*

	Median	Range	Elevated values	Normal level
Alkaline phosphatase	90	36–233	233	< 125 units/l
γ-Glutamyl transferase	21	7–94	94, 77	< 50 units/l
Glutamic–pyruvic transaminase	18	10–64	64	< 40 units/l
Bilirubin	9	6–17	17	< 15 μmol/l

Long-term follow-up revealed good results in 98 per cent of the patients in our series. No patient had signs or symptoms of biliary obstruction or infection, recurrent stones or stenosis of the common bile duct. Surviving patients had liver function tests which make the prospect of cholangitis very unlikely despite a few isolated increased values Follow-up studies after choledochoduodenostomy have also shown good results but the incidence of postoperative cholangitis has varied between 2 and 4 per cent[8–10]. The presumed lower incidence of cholangitis and sump syndrome following the Roux-en-Y technique is not proved and there are no data to support the superiority of choledochojejunostomy over choledochoduodenostomy[8,10,17]. We conclude that patients with bile duct stone with complex clearance of the bile duct can be safely treated by means of a choledochoenterostomy (in this study choledochojejunostomy), and long-term follow-up has shown good results and no signs or symptoms that could be associated with the drainage procedure.

Endoscopic sphincterotomy is now the procedure of choice in elderly and unfit patients and in patients who have retained stones or cholangitis. However, we still advise an internal drainage operation in younger patients undergoing surgery for cholelithiasis when common duct stones are found and where doubt exists about complete bile duct clearance (i.e. in patients with multiple small stones, sludge or gravel).

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Endoscopic endoprosthesis insertion following failure of cholecystojejunostomy in pancreatic carcinoma

J. F. Dowsett[*],
S. R. Cairns, D. Vaira,
A. A. Polydorou,
A. R. W. Hatfield and
R. C. G. Russell

Department of Gastroenterology,
The University College and
Middlesex Medical School,
London, UK
Correspondence to:
Dr J F Dowsett

Sixteen patients in whom malignant biliary obstruction recurred after failure of cholecystojejunostomy had attempted relief of obstruction by endoscopic insertion of an endoprosthesis. This treatment was successful in 13 patients, although one required percutaneous insertion because of duodenal distortion and one required a combined percutaneous–endoscopic approach. Median survival after stenting was 3·5 months (range from 2 weeks to 16 months). Of the three treatment failures, two patients had external drainage only and one succumbed before further treatment could be attempted. There were two complications associated with the procedure (one small bile leak and one episode of cholangitis) but the 30-day mortality rate of 12·5 per cent was related to disease progression rather than the procedure. Endoscopic stent insertion may achieve further worthwhile palliation of jaundice after the failure of surgery to relieve malignant biliary obstruction.

Keywords: Pancreatic cancer, obstructive jaundice, endoprosthesis

A wide variety of surgical procedures is performed to relieve malignant low common bile duct obstruction due to pancreatic adenocarcinoma[1]. Each has well recognized advantages and disadvantages[2] Cholecystojejunostomy is probably the quickest and easiest technical procedure when the gallbladder is dilated. The appreciable incidence of early failure due to synchronous cystic duct obstruction (often due to low insertion in the bile duct (*Figure 1*)) and late failure due to either metachronous cystic and/or proximal bile duct blockage or stomal stenosis (the former being much more common), has led many surgeons to avoid the operation when possible. Choledochoenterostomy is the initial operation preferred by some[3] and it has also been the surgical procedure of choice for early or late failure of cholecystojejunal anastomoses Secondary biliary procedures, however, probably carry a lower success rate and a higher complication rate than primary procedures We report our experience over the last 3 years with 16 consecutive patients with early or late failure of cholecystojejunal anastomoses who were managed by attempted endoscopic endoprosthesis insertion as an alternative to reoperation.

Patients and methods

Sixteen consecutive patients who had had cholecystojejunostomy performed for malignant low common bile duct obstruction due to adenocarcinoma of the pancreas had attempted treatment by endoscopic endoprosthesis insertion Failed endoscopic stenting was followed where appropriate by combined percutaneous–endoscopic stenting[4]. In three patients, the original surgery failed to provide adequate biliary drainage due to unrecognized malignant cystic duct occlusion (early failure) and in 13 cases biliary obstruction had recurred after initial successful surgical drainage (late failure). Patients with late failure were only treated if ultrasonography confirmed the presence of definite duct dilatation and the absence of significant intrahepatic metastatic disease. The median and mean time since surgery in the recurrent group was 9 months (range 3–24 months) Eight patients had histological proof of malignancy and in the remainder there was strong operative, ultrasound and endoscopic retrograde cholangiopancreatographic evidence of malignancy Patient parameters were mean age 62 years (range 43–79 years), mean bilirubin concentration 329 μmol/l (range 57–611 μmol/l, normal <17 μmol/l), mean albumin concentration 32 g/l (normal 35–53 g/l), mean urea concentration 4·3 mmol/l (normal 3·0–8·0 mmol/l) and mean haemoglobin concentration 10·3 g/l No patient had air in the bile ducts on ultrasound or plain abdominal X-ray. The gallbladder, however, was shown to be air-filled by these investigations in all patients, suggesting patency of the cholecystojejunal anastomosis (*Figure 2*) All endoscopic stents were inserted using the 4·2 mm channel Olympus TJF10 (Keymed, Southend, UK) endoscope and were 10 Fr in external diameter (*Figure 2*)

Results

Stent insertion was successful in 13 patients (81 per cent) with one being placed percutaneously because of duodenal distortion and one requiring a combined percutaneous–endoscopic procedure. Of the three failures, two patients had external drainage only after failed combined procedures and one deteriorated rapidly and had only a single endoscopic attempt at treatment before death (*Figure 3*). Two complications occurred (12 per cent) These were a small intraperitoneal bile leak after a combined procedure in one patient and, in another patient, cholangitis with septicaemia which developed after failed endoscopic retrograde cholangiopancreatography and settled with intravenous antibiotics and drainage by combined procedure. The 30-day mortality rate of 12 per cent (two patients) was entirely disease-related rather than procedure-related, although one of these patients had complete failure of drainage after dye injection (no combined procedure attempt). The two patients with external drainage survived 1·5 and 2·0 months. The median survival after stenting was 3·5 months (range from 2 weeks to 16 months) with a mean of 5 months. Survival is illustrated in *Figure 3*. Three patients required stent change before death

Discussion

More than 80 per cent of pancreatic adenocarcinomas are not amenable to surgical resection because of adverse tumour (metastasis, vascular invasion) or patient (multiple medical illness, advanced age) parameters[5] Palliation of pruritus, jaundice and pain is therefore usually the aim of therapy. Many forms of surgical biliary bypass have been described. Controversy exists about their relative merits and the

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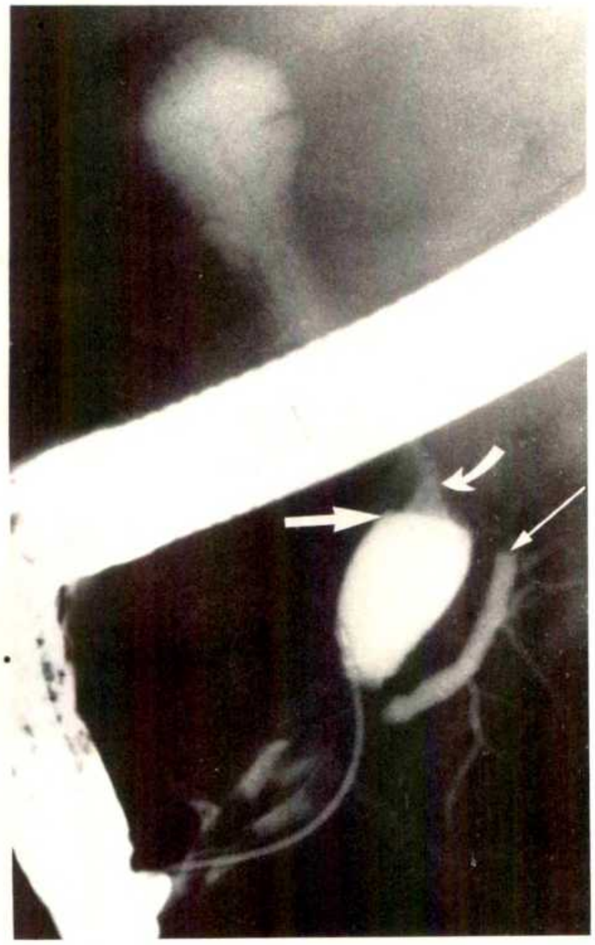

Figure 1 *Endoscopic retrograde cholangiopancreatography showing blocked pancreatic duct (thin arrow) and blocked bile duct (thick arrow) with cystic duct also occluded due to low entry into the bile duct (curved arrow)*

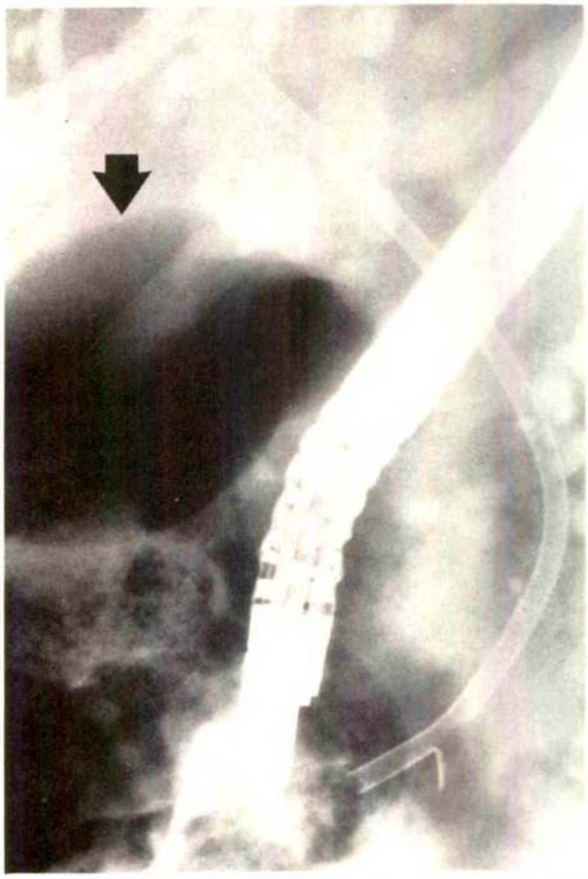

Figure 2 *Endoscopic retrograde cholangiopancreatography showing successful endoscopic stent insertion after failed cholecystojejunostomy; note air in adjacent gallbladder (arrow)*

desirability of prophylactic gastroenterostomy[6,7]. For low malignant common bile duct obstruction either the gallbladder or the common duct may be used for anastomosis. The two commonest operations performed are choledochojejunostomy and cholecystojejunostomy, although side-to-side choledochoduodenostomy is our own preference. Choledochojejunostomy often involves the formation of a Roux-en-Y loop and thus two anastomoses. The only important, though uncommon, late problem is anastomotic stricturing, which is not amenable to later endoscopic manipulation but can be managed by percutaneous transhepatic therapy. If the gallbladder is dilated, cholecystojejunostomy is possible and is undoubtedly technically simpler to perform than choledochoenterostomy. However, gallbladder dilatation does not definitely indicate cystic duct patency above the obstruction. Cholecystojejunostomy is limited by early and late cystic duct occlusion rather than anastomotic stenosis. Low cystic duct insertion predisposes to cystic duct blockage and may be deduced from plain X-ray or ultrasonography if air is present in the gallbladder but not in the biliary tree. However, as the biliary anatomy is basically unaltered, endoscopic intervention is still possible.

Internal biliary stenting has been possible by the percutaneous transhepatic route since 1978[8] and by the endoscopic route since 1980[9]. Randomized studies have suggested that drainage success rates and 30-day mortality rates are similar with surgery, percutaneous stenting or endoscopic stenting but that endoscopic stenting carries the least procedure-related morbidity[10-12]. As endoscopic stenting, if available, is a reasonable alternative to surgical palliation in fit patients and is probably the definite treatment of choice in unfit patients[13], a strong argument can be made for preferring

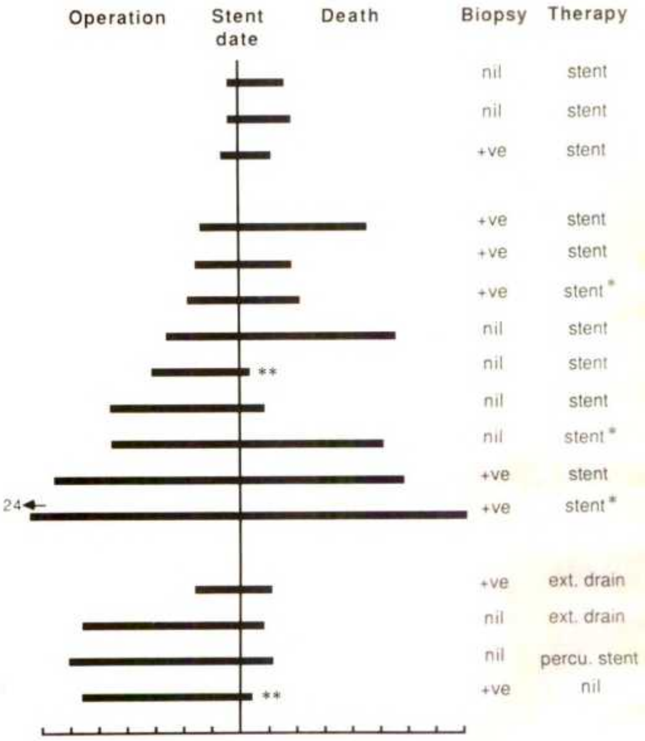

Figure 3 *Diagram of survival before and after stenting with details of histological confirmation and therapy achieved. The time before stenting is measured from the date of cholecystojejunostomy (operation) and the patients are divided into three groups: early failure, late failure with successful endoscopic stenting, and late failure with failed endoscopic stenting. * Stent change; ** died within 30 days*

endoscopic stenting to reoperation after failure of surgical biliary drainage when the bile duct is still accessible endoscopically. This review has shown that endoscopic stenting in this situation is safe and effective with a worthwhile median postprocedural survival time of 3·5 months.

Endoscopic stenting is a safe, successful alternative to reoperation for early or late failure after cholecystojejunostomy for malignant low common bile duct obstruction due to pancreatic carcinoma and should be offered as soon as surgical failure is recognized. Late failure is not necessarily a preterminal event and a further valuable period of jaundice-free survival may be obtained.

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Gallstone lithotripsy with the pulsed dye laser: in vitro studies

**A. Murray, R. Basu*,
P. D. Fairclough* and
R. F. M. Wood**

*Professorial Surgical Unit and
*Department of Gastroenterology,
St. Bartholomew's Hospital,
London EC1A 7BE, UK*

Correspondence to:
Mr A. Murray

The use of a pulsed dye laser to fragment human gallstones is reported. Laser energy was delivered by a 320 μm quartz fibre at wavelengths of 440, 480, 504, 560, 590, and 635 nm, in 1 μs pulses at energies of 5–60 mJ per pulse, producing peak powers of the order of 10^5 W. Cholesterol, pigment and mixed stones were fragmented. The shorter wavelengths were most efficient, using significantly less energy at 440 and 480 nm than at the longer wavelengths. Pigment stones were fragmented with significantly less energy than those in which cholesterol predominated. Thermal imaging during laser treatment showed no significant rise in temperature in the bulk of the stone. Absorption spectroscopy of bile revealed a peak at 450 nm, coinciding with the known absorption characteristic of bilirubin. Bile strongly attenuated light at shorter wavelengths, even at dilutions as great as 1:20 and protected samples of biliary epithelium from laser damage except when the optical fibre was in direct contact. The pulsed dye laser may offer significant advantages over current methods of biliary stone fragmentation.

Keywords: Choledocholithiasis, lithotripsy, laser surgery

Endoscopic sphincterotomy and stone extraction is successful in up to 90 per cent of patients with common duct stones, but fails if the stones are too large to pass through the sphincterotomy. In these cases there are several techniques being developed to fragment the stone before its removal. Mechanical lithotripsy, using a basket to crush the stone *in situ*, is relatively cumbersome and more complex methods such as ultrasonic, electrohydraulic and laser lithotripsy are being adapted from experience gained in treating stones within the renal tract[1,2]. Extracorporeal lithotripsy is being assessed for the fragmentation of gallbladder and common duct stones, but the indications and limitations are not yet clear and the devices are not widely available.

There are three types of laser in regular use in various fields of medicine: the argon, neodymium YAG and carbon dioxide devices. Each produces a continuous laser beam of a specific wavelength that achieves its effect by heating the target tissue. A purely thermal mechanism, however, will not fragment gallstones. Teng *et al.*[3] have shown that by pulsing laser energy in short, high energy bursts an 'acoustic' shock-wave effect is produced that can effectively fragment stones. Lux *et al.*[4] reported the first successful endoscopic retrograde laser lithotripsy in man in 1986 and have recently published a total of eight further cases[5]. They used a *pulsed* neodymium YAG laser which produces light in the near infrared part of the spectrum (1064 nm). Light at this wavelength has a low absorption:scattering ratio which results in poor absorption and high penetration through tissues. As biliary stones have a variable bile pigment content it may be possible to take advantage of enhanced absorption of light at shorter wavelengths by these pigments and thus reduce the energy necessary for fragmentation and thereby increase the safety margin.

Biliary stones are a heterogeneous group, varying in cholesterol, bile pigment and calcium salt content. They lie in an area of delicate anatomy in which thermal or mechanical damage to the biliary structures must be avoided and the margin for error during therapeutic manoeuvres is small. It is therefore imperative, if using a laser within the biliary tree, to choose the most efficient device in terms of wavelength, fragmentation energy and safety.

We report *in vitro* experiments of gallstone fragmentation and bile absorption using a pulsed dye laser at six wavelengths across the visible spectrum, to determine the most efficient and safe laser parameters.

Materials and methods

Stone fragmentation

A total of 55 biliary calculi were collected from ten patients each having five or more stones. The stones were weighed, their maximum diameter measured with an engineering micrometer and they were then stored dry, in sealed containers. The stones from each patient were randomly allocated one to each of six groups. Two groups contained ten stones, three groups had nine and one had eight.

Pulses of laser energy, each of 1 μs duration, were generated by a xenon flashlamp-pumped pulsed dye laser (Model MDL-1P, Candela Laser Corporation, Wayland, Massachusetts, USA). Six wavelengths were produced sequentially using 2×10^{-4} M solutions of six organic laser dyes: coumarin (440, 480, and 504 nm), rhodamine (560 and 590 nm) and DCM (635 nm) (Exciton, Dayton, Ohio, USA). Each group of stones was subjected to laser energy at one of the above wavelengths. The energy was conducted to each stone by a 1·5 m length of a 320-μm core, step-index flexible optical fibre. This was held in direct contact with the stone by a counterbalanced arm weighted to 10 g. Each stone was supported in turn on a gelatin mould within a polythene flask and immersed under 1 cm of saline. Energy was delivered as a series of 1 μs pulses at a rate of 10 pulses per second. The initial pulse energy was 5 mJ, increasing by increments of 5 and then 10 mJ every 100 pulses, up to a maximum of 60 mJ per pulse. This resulted in an energy density (energy per unit area) at the fibre tip of 6·75–75 J cm^{-2} and a peak pulse power of the order of 10^5 W. The total energy at which gross fragmentation occurred was recorded. The average power output was monitored before and after the delivery of each energy increment by a Coherent 210 power meter (Coherent, Palo Alto, California, USA).

Stone analysis

Quantitative stone analysis was performed on the fragments resulting from lithotripsy. After grinding to a powder, the cholesterol fraction was extracted with ether. The calcium salts were extracted by passage through concentrated hydrochloric acid, leaving a residue composed of bile pigments. The dry sample weight was measured at each stage.

Absorption spectroscopy of bile

Six samples of bile were collected from patients undergoing cholecystectomy. After storage at 4°C for up to 48 h, a 4-ml portion of each sample was subjected to absorption spectroscopy between 350 and 1100 nm, with a Shimadzu UV 160 spectrophotometer (Shimadzu Corporation, Duisberg, DDR). This determined the typical absorption

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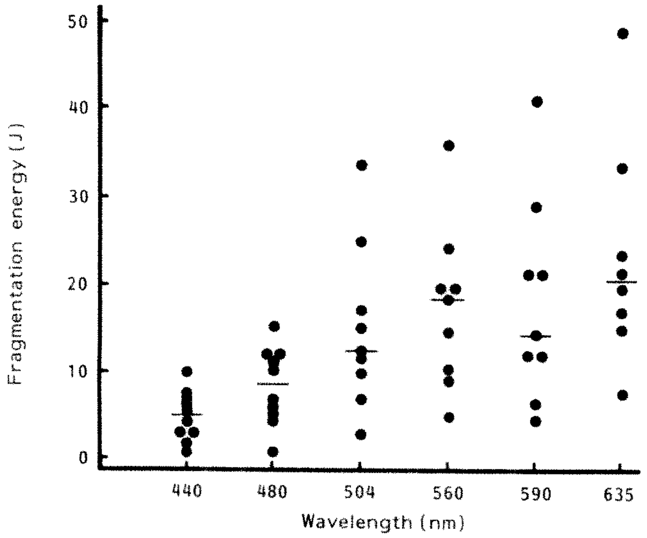

Figure 1 *Fragmentation energy at six wavelengths for each of 55 gallstones. The total energy (J) to fragment each stone is plotted against wavelength (nm)*

characteristics over the whole range of the visible spectrum and, in particular, at those wavelengths used in these experiments.

Attenuation of laser light by bile

To investigate the attenuation of laser light at varying bile concentrations, further 4-ml samples were diluted with known volumes of normal saline. Aliquots of 1 cm^3 were held in a 1 cm^2 polished glass cuvette, the base of which was placed on a glass coverslip in contact with the sensing face of the power meter. Laser energy, at a wavelength of 480 nm, was conducted to the sample by a 320 μm diameter flexible optical fibre held in a micromanipulator. The power transmission was measured at bile dilutions of 1:10, 1:20, 1:40 and 1:100, at pulse energies of 20–100 mJ, in 20-mJ increments.

Tissue damage and the effect of bile

Human gallbladder and bile duct specimens were obtained from fresh cadavers. The tissues were then cut into 1 cm^2 samples and exposed to laser energy conducted by the 320 μm optical fibre held in a micromanipulator at distances of 1, 2, 3, 4 and 5 mm from the epithelial surface. Exposures of 100 pulses were then made at pulse energies of 20, 40, 60, 80 and 100 mJ, with the samples immersed both in saline alone or known dilutions of bile. Each specimen was snap-frozen and sectioned in a cryotome. The depth of any crater resulting from ablation by the absorption of the laser energy was measured with optical micrometry. A proportion of sections were stained with haematoxylin and eosin and then examined under light microscopy for signs of thermal damage.

Thermography

To document the temperature changes in stones undergoing fragmentation, high resolution thermographic images were recorded using a Thermovision 870 infrared camera system (Agema, Leighton Buzzard, UK). The camera was focused on the fibre–stone interface in air. The laser was fired at a range of energies from 20 to 60 mJ to produce stone fragmentation. The resulting infrared image was recorded digitally to enable an accurate estimation of the surface temperature of the bulk of the stone adjacent to the point of fragmentation.

Results

Stone fragmentation

The 55 stones subjected to laser lithotripsy were of median weight 2·1 g (range 0·5–3·5 g) and median maximum diameter 1·6 cm (range 0·7–2·1 cm). In all, ten stones were fragmented at a wavelength of 440 and ten at 480 nm, nine stones were fragmented at 504 nm, nine at 560 nm, nine at 590 nm and eight at 635 nm. There were no significant differences in the weights of the stones between groups. Fragmentation was achieved with a wide range of energy, from a threshold energy of 20 mJ per pulse for predominantly pigment stones at the 440 nm wavelength, to energies of 60 mJ at the longer wavelengths.

Typically the fibre drilled into the stone at sub-fragmentation energy after which gross fragmentation was achieved at the next energy increment. The resulting fragments were of varying size, usually comprising two or more large fragments with multiple small particles. The median maximum diameter of the largest fragment from each stone was 0·81 cm (range 0·45–1·05 cm). During fragmentation, a 'cracking' sound was audible with each laser pulse over 20 mJ in energy. The total fragmentation energy for each stone at each wavelength is plotted in *Figure 1*. As the wavelength was increased, the energy necessary to achieve fragmentation also increased. When compared with the fragmentation at 440 nm, the energies required were significantly greater at 504 nm ($P<0·05$) and at 560, 590 and 635 nm ($P<0·01$). At 480 nm the energy was significantly less than at 560, 590 and 635 nm ($P<0·01$, Wilcoxon rank sum). Fragmentation was most efficient therefore at the shorter wavelengths. No macroscopic damage to the delivery fibre was observed during the fragmentation, although microscopic examination showed roughening of the previously cleaved surface suggestive of local mechanical trauma.

Stone analysis

Stone analysis revealed a cholesterol content of 22–93 per cent, a bile pigment content of 2–62 per cent and calcium salt content of 4–16 per cent. Fragmentation energy varied with stone composition. Stones composed largely of bile pigment were fragmented with a median energy of 2·2 J (range 0·7–6·5), which was significantly less energy than the median of 24·2 J (range 10·4–71 J) required to break stones composed predominantly of cholesterol ($P<0·01$, Wilcoxon rank sum).

Absorption spectroscopy of bile

Bile spectroscopy typically revealed a biphasic absorption maximum between 300 and 500 nm (*Figure 2*), the second peak coinciding with the peak absorption of bilirubin at 453 nm. Ascending through the visible spectrum the absorption decreased rapidly above 500 nm reaching a minimum in the infrared.

Attenuation of laser light by bile

Bile was found to strongly attenuate laser energy at the shorter wavelengths. The attenuation at 480 nm by known dilutions of six samples of bile are plotted in *Figure 3*. Complete absorption of energy was found with dilutions up to 1:10 in all samples. At dilutions greater than 1:10 there was measurable absorption even in dilutions as great as 1:100.

Tissue damage and the effect of bile

Craters discernible to the naked eye were created at all laser energies when the optical fibre was held in contact with each

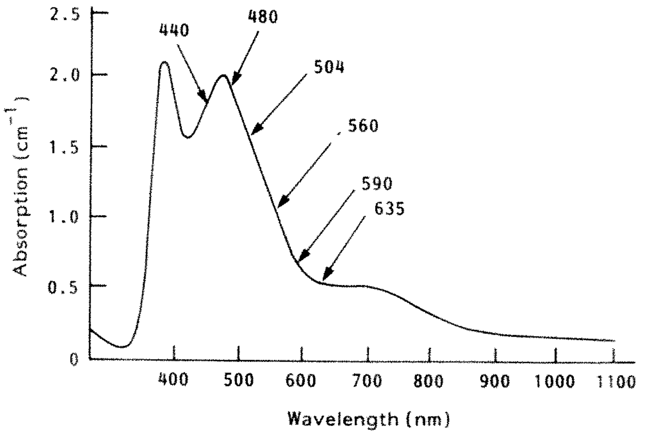

Figure 2 *Typical absorption spectrum of human bile with lithotripsy wavelengths superimposed. The absorption (cm^{-1}) is plotted against wavelength (nm)*

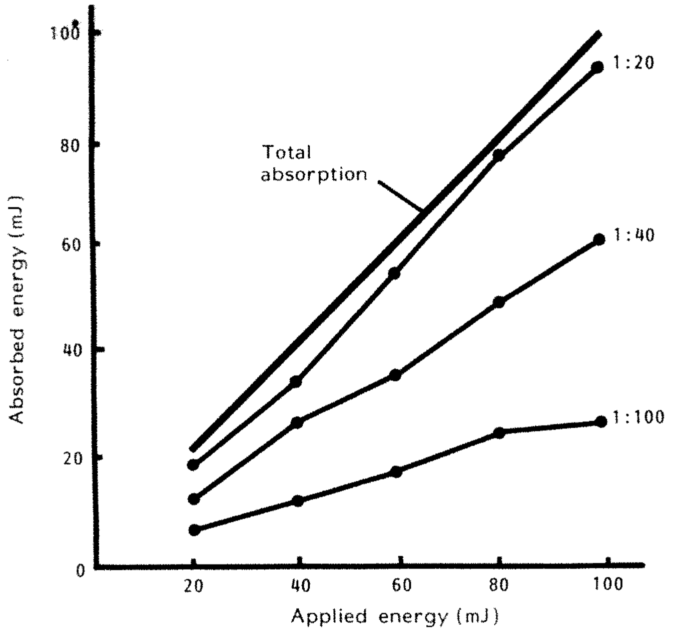

Figure 3 *Attenuation of 480 nm laser energy by bile dilutions of 1:20, 1:40 and 1:100. Each point represents the median of absorbed energy of six samples of human bile and is plotted against incident pulse energies of 20, 40, 60, 80 and 100 mJ*

specimen. The diameter of the craters matched that of the fibre. On light microscopy the lesions had a well defined edge, without signs of burning or charring and with no surrounding zone of thermal coagulation. All these features are consistent with the effects known to be produced by pulsed lasers. Craters also occurred when the fibre was held under saline, at up to 3 mm distance from the epithelium at energies above 40 mJ per pulse. Crater depth, as measured by optical micrometry, increased with duration of exposure and pulse energy. When immersed in undiluted bile, craters occurred only when the fibre was in contact with the epithelium, thus effectively excluding bile from the interface. With the fibre held at 1 mm distance from the epithelium, craters were only produced at pulse energies of 20 mJ and above, and at bile dilutions of more than 1:10. At greater distances, even in very dilute bile, the beam divergence and absorption led to a power density that was insufficient to produce discernible craters.

Thermography

Thermographic imaging confirmed that the bulk of the stone does not undergo a measurable temperature rise during laser fragmentation, even when supramaximal energies of 100 mJ were used in air. A rise of between 10 and 20°C was recorded immediately adjacent to the point of fibre-penetration of three stones tested. The remainder of the surface of the stone showed no temperature rise up to and beyond the moment of fragmentation.

Discussion

This study confirms that human gallstones can be reliably fragmented by laser energy from a pulsed dye laser at a range of wavelengths across the visible spectrum.

Simple modifications of current methods of basket extraction, with a central channel in the catheter for the optical fibre, will allow this contact technique to be applied *in vivo*.

Burhenne heralded the non-surgical management of common duct stones when, via a T tube track, he fragmented a common duct stone with an electrohydraulic probe[6] and went on to treat many hundreds of patients with the aid of this technique[7]. The use of laser energy within the bile duct is a natural progression from this work. The ability to couple laser energy to fine flexible optical fibres of a diameter of <0·5 mm is ideally suited to an endoscopic approach and compares very favourably with the probe diameters of up to 3 mm for current electrohydraulic methods.

Lux *et al.* have reported *in vitro* work on lithotripsy using a neodymium YAG laser which produces a pulse of relatively long duration (0·1–10 ms) at a wavelength of 1064 nm. They report a median fragmentation energy of 32 J for stones < 1·5 cm in diameter, and 80 J for those > 1·5 cm. The energies necessary for fragmentation of comparable stones with the pulsed dye laser at short wavelengths are of the order of 6–10 times less.

Pulsed laser energy has to be applied directly to the stone surface for a reliable effect to be achieved. Fragmentation required significantly less energy at the shorter wavelengths (440–480 nm) than at the longer (504, 560, 590 and 635 nm). At 440 nm the median fragmentation energy was four times less than that required at the longest wavelength (635 nm). Stone particles resulting from fragmentation tended to be of a relatively large size and would in some cases need further fragmentation before successful extraction. Predominantly pigment stones required significantly less energy for fragmentation than those of a mixed or largely cholesterol content ($P < 0{\cdot}01$). It is the bilirubin content of gallstones that leads to their more efficient fragmentation at shorter wavelengths. There are few published data on light absorption by gallstones. Leung *et al.*[8] have shown that at 700 nm the absorption coefficients of cholesterol and pigment stones are 30 and 100 cm^{-1}, such that pigment stones, being more highly absorptive, would fragment at lower energies. The results in this paper would suggest that the differential absorption between predominantly cholesterol or pigment stones holds good across the spectrum. Cholesterol stones are still effectively broken up by the pulsed dye laser, as the acoustic shockwave production is a function of the high peak power of the pulse, which is then further augmented in the pigment-containing stones. The short pulse length of the pulsed dye laser (1 μs) as compared with the YAG device (10^2–10^3 μs) produces a higher peak power for a given pulse energy and thus an improved fragmentation efficiency. The YAG laser is therefore less than ideal for the production of the optimal conditions for lithotripsy.

The exact mechanism of action of pulsed lasers in stone fragmentation is still under debate, but it appears that above a certain threshold the high peak energy concentrated on a very small area of the stone surface results in the instantaneous production of a plasma of ionized molecules lasting for a fraction of a second. The expansion of this plasma then produces stress waves that propagate through the stone, resulting in cleavage at planes of structural weakness. This process would account for the necessity for contact between the fibre and the stone for effective fragmentation to be achieved. The audible 'crack' is thought to result from the plasma production. Shorter wavelengths are more efficient as they are better absorbed by the stone constituents and thus lower the energy requirements for the production of plasma formation. Stone fragmentation is more effective under fluid as this compresses the shockwave in the direction of the stone. Spectroscopy of samples of human bile revealed a peak centred on the maximum absorption of bilirubin at 453 nm. Bile around a stone will strongly absorb any stray laser light, thus decreasing the risk of laser-induced damage to the bile duct. We have shown that even when greatly diluted, as would be the case when contrast media are injected into the duct to facilitate control, bile will effectively absorb laser energy. At a dilution of 1:20, a 1 cm depth (equivalent to a depth of neat bile of 0·5 mm), laser energy at up to 100 mJ, at the 480 nm wavelength, is 95 per cent absorbed and this degree of protection avoids laser damage to biliary epithelium *in vitro*.

Thermal imaging has confirmed that there is an insignificant temperature rise of the stone even when fragmented at high energies in a thermally insulating air medium. Infrared imaging is only capable of defining surface temperature and cannot measure temperatures deep within the stone. However, there are sound physical arguments against there being a significant thermal rise, because of the particular pulse parameters used. Because the pulse duration of 1 μs is very short when compared with the period between pulses (100 ms at a pulse repetition rate of 10 Hz), any heat produced with each laser pulse has time (the characteristic thermal relaxation time) to dissipate before the next pulse arrives. Thus there is no significant relentless rise in temperature during laser treatment which would be found if a continuous wave laser was used. This has important implications for avoiding thermal damage to surrounding biliary structures during *in vivo* laser treatment.

Pulsed dye laser energy will damage biliary epithelium if the fibre is held in direct contact while firing for many seconds, but this is unlikely to occur when the laser fibre is in contact with the stone in a bile medium. If a lesion is produced in the duct wall, there is no thermal damage to the surrounding tissues because of the short-pulsed nature of the energy.

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Measurement of body water compartments after ligation of the common bile duct in the rabbit

F. Martínez-Ródenas, L. M. Oms, X. Carulla, M. Segura, J. J. Sancho, C. Piera*, M. R. Fernández-Espina* and A. Sitges-Serra

*Department of Surgery and Surgical Research Unit, Hospital del Mar, Institut Municipal d'Investigacions Mèdiques and *Department of Nuclear Medicine, Hospital Clínic i Provincial, University of Barcelona, Barcelona, Spain*

Correspondence to:
A. Sitges-Serra, Servicio de Cirugía, Hospital Universitario del Mar, Paseo Marítimo, 25–29, 08003 Barcelona, Spain

To elucidate the pathogenesis of renal insufficiency associated with obstructive jaundice we have studied spontaneous water intake and body water compartments in rabbits undergoing common bile duct ligation. Total body water, extracellular water and plasma volume were measured by multi-isotope dilution technique. During the initial 6 postoperative days spontaneous water intake was 898 ml in sham operated animals (SO) but only 280 ml in jaundiced rabbits (OJ6) (P < 0·01). *Creatinine clearance was almost unchanged in SO but fell to 60 per cent of the preoperative values both in OJ6 and in paired-drink sham operated animals (SO2). There was a 15 per cent decrease in total body water* (P < 0·01) *and a 24 per cent decrease in extracellular water* (P < 0·01) *6 days after bile duct ligation. There was a further reduction of the extracellular water to 35 per cent and a 15 per cent reduction of plasma volume 12 days after ligation. Water restriction mimicked the alterations in body composition produced by bile duct ligation. We conclude that bile duct ligation is associated with hypodypsia and a depletion of extracellular water and plasma volume. These alterations could explain the tendency to develop hypotension and renal failure which are associated with obstructive jaundice.*

Keywords: Obstructive jaundice, renal failure, fluid compartments

Although several measures have been proposed to prevent postoperative renal failure in obstructive jaundice up to now none has gained widespread acceptance. Recently published randomized clinical trials have failed to confirm the value of mannitol[1] or oral administration of bile salts[2] in preventing renal function deterioration in this setting. Newer methods are also likely to fail since the pathogenesis of renal failure in obstructive jaundice has not been clearly elucidated. Several observations have indirectly shown that water depletion may play a fundamental part[1–6]. However, no studies have been carried out to measure directly the water balance and fluid compartments in obstructive jaundice. Accordingly in the present article we report studies of water intake, renal function and body composition in rabbits undergoing ligation of the common bile duct aiming at disclosing changes in body water compartments induced by biliary obstruction.

Materials and methods

California male rabbits with a mean weight of 2700 g (range 2490–3000 g) were used in all experiments. To allow for adaptation the animals were kept in metabolic cages on arrival from 7 days before the study to its end. The experiment was carried out in two phases. First, water balance and renal function were determined before and 6 days after surgery in three groups of rabbits: sham operated (group SO, $n = 8$), common bile duct ligated (OJ6, $n = 8$) and a sham operated group that was offered the same amount of water and chow as that drunk and eaten by jaundiced rabbits (group SO2, $n = 8$). Diuresis and water intake were recorded daily. Urine and plasma osmolarity were determined on day 6. Creatinine clearance was measured using standard techniques.

In a second phase, body composition studies were carried out in four different groups of animals. In group SO ($n = 7$) body composition was assessed before and 6 days after a sham operation, in group OJ6 ($n = 8$) body composition was assessed before and 6 days after bile duct ligation, in group OJ12 ($n = 6$) body composition was assessed before and 12 days after ligation and, finally, in group SO2 ($n = 8$) body composition studies were carried out before and after a sham operation after which animals were paired-drunk and paired-fed with OJ6 rabbits.

Double ligation of the common bile duct was performed through a midline incision under general anaesthesia with ketamine (10 mg/kg) and diazepam (2 mg/kg) intramuscularly and halothane (1–3 per cent). In sham operated animals a midline incision, under the same type of general anaesthesia, was also performed and the common bile duct was dissected free but not ligated. Thus, the duration and visceral handling in sham operated animals was very similar to that of animals undergoing bile duct ligation. Cefonicid (125 mg) was administered intramuscularly 1 h before surgery and 24 h and 48 h after the intervention. At the end of the experiment, animals were killed and autopsies performed. In all animals the state of the common bile duct was assessed, particularly in animals belonging to groups OJ6 or OJ12 in which dilatation of the ligated bile duct was confirmed.

The weight of the rabbits was determined daily and the mean of three repeated measurements was recorded. For the determination of total body water, extracellular water and plasma volume the following three solutions were prepared: 740 kBq/ml $^{3}H_2O$ (Ire Medgenix, Belgium), 740 kBq/ml $^{35}SO_4$ and 74 kBq/ml ^{125}I-labelled albumin (Amersham International, Amersham, UK). First, 0·5 ml (370 kBq) of tritiated water and radiosulphate were injected through the marginal vein of the ear. After 3 h a 5-ml arterial blood sample was obtained and plasma was promptly separated and deproteinized by adding 10 per cent trichloroacetic acid (2 ml plasma/4 ml acid)[7]. This plasma was used to measure the ^{3}H and $^{35}SO_4$ radioactivity. Then 0·5 ml (37 kBq) ^{125}I-labelled albumin solution was injected and 10 min later another 5 ml arterial blood sample was obtained for counting the ^{125}I radioactivity. For the postoperative study the same procedure was applied but a basal serum sample was obtained to subtract the remaining radioactivity.

To determine the total radioactivity of ^{3}H and $^{35}SO_4$ administered, standard solutions of 0·5 ml of the isotope solutions in 100 ml of distilled water were prepared. Then 1 ml of these solutions was dissolved in 10 ml of deproteinized rabbit plasma obtained from rabbits with jaundice (OJ6, $n = 5$, OJ12, $n = 5$) or controls ($n = 5$) to prepare standard solutions with a similar degree of quenching to those of the serum samples. This 1/1000 solution was used for β counting. The total radioactivity of the administered ^{125}I-labelled albumin was calculated diluting 0·5 ml of the stock solution in 100 ml distilled water. All the counting procedures were carried out in triplicate. ^{3}H and $^{35}SO_4$ radioactivity was measured after dissolving the deproteinized serum samples in 13 ml scintillation liquid (Scintran,

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BDH Chemicals Ltd., Poole, UK) in a LKB 1217 Rackbeta (LKB Wallac, Turku, Finland). ^{125}I-labelled albumin radioactivity was measured in a Packard 800C (Packard, USA) counter. Body water compartments were measured using the following formulae in which we assumed a Donnan factor of 0·93 and a plasma protein concentration of 0·9 g/l. In the first two formulae, the number 3 represents a dilution coefficient:

$$\text{Total body water} = \frac{\text{d.p.m/ml } ^3H_2O \text{ (standard)} \times 1000 \times 0{\cdot}93}{\text{d.p.m./ml } ^3H_2O \text{ (plasma)} \times 3}$$

$$\text{Extracellular water} = \frac{\text{d.p.m./ml } ^{35}SO_4 \text{ (standard)} \times 1000 \times 0{\cdot}93 \times 0{\cdot}9}{\text{d.p.m./ml } ^{35}SO_4 \text{ (plasma)} \times 3}$$

$$\text{Plasma volume} = \frac{\text{c.p.m./ml } ^{125}\text{I-labelled albumin (standard)} \times 100}{\text{c.p.m./ml } ^{125}\text{I-labelled albumin (plasma)}}$$

We did not calculate the urinary excretion of the isotopes to simplify the calculations. Intracellular water and interstitial water were indirectly obtained from the measured compartments. Sizes of body water compartments are expressed in absolute numbers and as percentages of the basal values to minimize the influence of the body weight which was slightly lower in group OJ12 compared with the remaining three groups. Comparisons between groups were carried out with the analysis of variance test for grouped non-parametric samples (Kruskal–Wallis) and differences between single groups with the Mann–Whitney *U* test for unpaired data. Pearson's correlation coefficient was used to assess the relationship between different variables. Statistical significance was accepted if $P<0{\cdot}05$ when calculated for two tails.

Results

Water intake and renal function

The results are shown in *Table 1*. During the 6 days of the experiment, OJ6 rabbits drank a mean of 280 ml water whereas SO rabbits drank 898 ml ($P<0{\cdot}01$). The percentage of body weight loss was significantly higher in groups OJ and SO2. The percentage fall in creatinine clearance was similar in groups OJ6 and SO2 and was significantly greater from that of group SO ($P<0{\cdot}01$). In spite of a similarly reduced water intake, the OJ6 rabbits had a lower urine osmolarity than the water restricted animals.

Table 1 *Water balance and renal function in sham operated, jaundiced and sham operated paired-drunk rabbits 6 days after surgery*

	SO ($n=8$)	OJ6 ($n=8$)	SO2 ($n=8$)	*P*
Basal weight (g)	2660 ± 99	2607 ± 105	2745 ± 103	n.s.
Weight loss (%)	5·7 ± 2	14·0 ± 4·3	13·0 ± 2	<0·01
Water intake (ml)	898 ± 221	280 ± 146	280 ± 0	<0·01
Diuresis (ml)	604 ± 181	316 ± 57	238 ± 59	<0·001
Urine osmolarity (mOsm/l)	817 ± 417	935 ± 288	1373 ± 373	<0·02
Plasma osmolarity (mOsm/l)	286 ± 11	293 ± 19	290 ± 26	n.s.
Chow intake (g)	363 ± 57	57 ± 85	57 ± 0	<0·01
Bilirubin (μmol/l)	3·4 ± 1·7	153 ± 48	3·4 ± 0·8	<0·01
% Fall creatinine clearance	+4 ± 36	−37 ± 19	−44 ± 28	<0·01

SO, sham operated; OJ6, jaundiced; SO2, sham operated paired-drunk; n.s., not significant (Kruskal–Wallis non-parametric analysis of variance). By non-parametric comparison there were no differences between groups OJ6 and SO2

Body composition

The basal preoperative body composition of all groups is shown in *Table 2*. There were significant changes in body water compartments 6 days after common bile duct ligation. Weight loss was greater in OJ6 than in SO rabbits (14 *versus* 6 per cent, $P<0{\cdot}0002$). In group OJ6 weight loss closely correlated with total body water loss during the same period ($r^2=0{\cdot}82$, $P<0{\cdot}0001$, *Figure 1*). When compared with group SO, OJ6 rabbits showed a greater reduction in total body water mainly owing to a reduction of the extracellular fluid compartment (*Table 3*). When group OJ6 was compared with group OJ12, a further and significant reduction in the extracellular fluid compartment was appreciated which was associated with a 15 per cent decrease in plasma volume (*Table 4*). In spite of the depletion of the extracellular compartment, intracellular water was normal at this stage, a fact consistent with isotonic extracellular fluid loss. The paired-drunk sham operated rabbits showed alterations of body composition similar to those of rabbits undergoing bile duct ligation (*Table 5*).

Discussion

Although the histological appearance of kidneys of patients dying of acute renal failure associated with obstructive jaundice closely resembles that associated with hypovolaemic shock[8], no satisfactory explanation has been proposed to link this phenomenon with biliary obstruction and the true cause of renal dysfunction in this setting has not yet been firmly

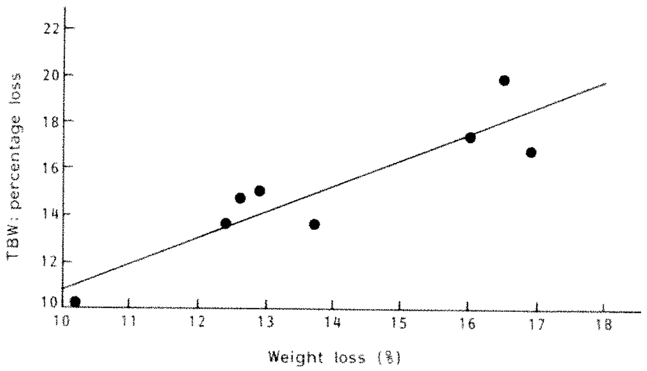

Figure 1 *Correlation between weight loss and total body water (TBW) loss in rabbits 6 days after common bile duct ligation; values are expressed as percentages of the basal preoperative measurements. y = 1·135x − 0·538, r² = 0·82, P < 0·001*

Table 2 *Basal preoperative values of body water compartments in sham operated, sham operated and paired-drunk and jaundiced rabbits*

	SO ($n=7$)	SO2 ($n=8$)	OJ6 ($n=8$)	OJ12 ($n=6$)	*P*
Total body water	1979 ± 148	2043 ± 1550	1974 ± 174	1950 ± 166	n.s.
Intracellular water	1015 ± 131	1102 ± 136	1136 ± 134	986 ± 170	n.s.
Extracellular water	963 ± 133	941 ± 11	837 ± 88	964 ± 130	n.s.
Interstitial water	868 ± 131	850 ± 84	753 ± 87	884 ± 128	n.s.
Plasma volume	95 ± 8	91 ± 11	94 ± 14	88 ± 8	n.s.

Values are mean ± s.d. expressed as millilitres of water; SO, sham operated; SO2, sham operated paired-drunk; OJ6, jaundiced, assessed 6 days after bile duct ligation; OJ12, jaundiced, assessed 12 days after bile duct ligation; n.s., not significant (Kruskal–Wallis non-parametric analysis of variance test)

Table 3. *Size of body water compartments in sham operated and jaundiced rabbits 6 days after surgery*

	SO (*n* = 7)	OJ6 (*n* = 8)	*P*
Total body water	1857 ± 186 (−6)	1675 ± 162 (−15)	<0·05
Intracellular water	905 ± 105 (−10)	1043 ± 139 (−8)	<0·05
Extracellular water	955 ± 147 (−0·6)	632 ± 58 (−24)	<0·01
Interstitial water	855 ± 134 (−1)	549 ± 57 (−26)	<0·01
Plasma volume	108 ± 11 (15)	94 ± 8 (−1)	<0·01

Values are mean ± s.d. expressed as millilitres of water; SO, sham operated; OJ6, jaundiced; numbers in parentheses are the mean percentage increase or decrease of each compartment in respect to its preoperative value; statistical significance calculated using Mann–Whitney *U* test

Table 4 *Size of body water compartments in jaundiced rabbits 6 and 12 days after surgery*

	OJ6 (*n* = 8)	OJ12 (*n* = 6)	*P*
Total body water	1675 ± 162 (−15)	1577 ± 123 (−18)	n.s.
Intracellular water	1043 ± 139 (−8)	955 ± 114 (−2)	n.s.
Extracellular water	632 ± 58 (−24)	621 ± 38 (−35)	<0·05
Interstitial water	549 ± 57 (−26)	534 ± 48 (−34)	<0·01*
Plasma volume	94 ± 8 (−1)	76 ± 6 (−15)	<0·01*

Values are mean ± s.d. expressed as millilitres of water; OJ6, jaundiced, assessed 6 days after bile duct ligation; OJ12, jaundiced, assessed 12 days after bile duct ligation; numbers in parentheses are the mean percentage increase or decrease of each compartment in respect to its preoperative value. * Owing to technical difficulties only three rabbits in the OJ12 group could be used for these two calculations; n.s., not significant (Mann–Whitney *U* test, concerning the differences in percentage decrease for each compartment and not the absolute values in millilitres, in order to minimize the influence of body weight which was slightly lower in OJ12 group (2783 *versus* 2557 g, $P < 0·05$))

established. Several hypotheses have been developed to explain the pathogenesis of this complication. These can be broadly classified into three main lines of thought: nephrotoxicity of bile components, haemodynamic alterations and harmful effects of endotoxin. The nephrotoxicity theory holds that some substances that are usually excreted through the bile tend to accumulate in plasma when bile flow is interrupted. When excreted through the kidney these could have either a direct nephrotoxic effect or 'sensitize' the kidney to the action of other factors that can cause renal damage. Substances that have been implicated are the IgA immunoglobulins[9], bile salts[10] and conjugated bilirubin[11]. A recent review by Green *et al.*[12] summarizes the work done in the field of the 'haemodynamic alterations' theory. Briefly, cholaemia would impair left ventricular performance, diminish vascular tone and/or impair the responsiveness to sympathetic vasoconstrictor influences thus explaining the increased susceptibility to shock in obstructive jaundice.

Bailey[13] proved the presence of endotoxaemia in rats and in man during obstructive jaundice and advanced the hypothesis that this might be related to increased bowel absorption of endotoxin due to the absence of bile salts. Endotoxin would result in renal damage either by intrarenal activation of the coagulation cascade, leading to a localized intravascular coagulation, or through haemodynamic alterations. Some studies have suggested that oral administration of bile salts to prevent endotoxin absorption[14–16] or of lactulose to reduce bacterial proliferation in the bowel lumen[17] might prevent renal function deterioration in obstructive jaundice. Recently, however, a clinical randomized trial has failed to prove any benefit from the preoperative administration of ursodeoxycholic acid[2] and further studies are still required to prove the clinical usefulness of these treatments.

The aforementioned hypotheses linking renal failure and obstructive jaundice have failed to emphasize the role of water depletion which, in our view, is the final common pathway leading to impairment of renal function. Topuzlu and Stahl[18] were the first to suggest that renal impairment in obstructive jaundice could be caused by hypovolaemia after they induced a water and sodium diuresis in the dog following intravenous injection of bile. Williams *et al.*[3] demonstrated that in jaundiced dogs the amount of haemorrhage necessary to induce hypovolaemic shock was much less than in control animals. Hishida *et al.*[4] showed, in a rabbit model, that 10 days after common bile duct ligation there was evidence of secondary hyperaldosteronism. Cioffi *et al.*[6] found that the perfusion pressure of the isolated 'jaundiced kidney' in rabbits with ligated common bile ducts was superior to that of sham operated animals. We interpret all these studies as providing indirect proof of volume depletion. However, to date, no systematic studies have been carried out to investigate the body water compartments in obstructive jaundice. The only work specifically devoted to measure blood volume in obstructive jaundice was that published in 1971 by Gillet[19]. He measured plasma volume using radioiodinated albumin 8 days after common bile duct ligation in rats and was able to show that it was reduced by 15 per cent.

Using a multi-isotope dilution technique to measure body water compartments we have found that 6 days after common bile duct ligation there is a 15 per cent reduction of total body water mostly owing to depletion of the extracellular compartment. At this stage, body weight closely correlated with the degree of water loss. The plasma volume remained unaffected but did not show the physiological expansion observed in sham operated animals. Twelve days after common bile duct ligation there is a further reduction, up to 35 per cent, of the extracellular fluid compartment which then became associated with a 15 per cent decrease of plasma volume. The intracellular water remained almost unaffected throughout the period of the investigation probably because no osmotic changes occurred in the extracellular compartment.

At a later stage, 12 days after common duct ligation in our model, reduction in plasma volume ensues. This may result in reduced renal blood flow probably making the kidney more sensitive to any kind of insult. Preliminary studies in our laboratory have shown a significant reduction of renal plasma flow, assessed by para-aminohippurate clearance, as soon as 4 days after bile duct ligation.

The causes of volume depletion are to be found in a deterioration of the renal mechanisms of water and sodium preservation and in the lack of water and sodium intake. In the first phase study we found that 6 days after bile duct ligation, jaundiced animals excrete a more dilute urine than their sham operated counterparts despite being volume depleted. In unpublished observations we found that administration of saline to jaundiced animals, despite some protective effect on creatinine clearance, is followed by brisk diuresis indicating their inability to retain water and salt. Hypodypsia may also be an important factor leading to negative water balance in obstructive jaundice. Spontaneous water intake was much

Table 5 *Size of body water compartments in jaundiced rabbits and paired-drunk controls 6 days after surgery*

	OJ6 (*n* = 8)	SO2 (*n* = 6)	*P*
Total body water	1675 ± 162 (−15)	1735 ± 98 (−15)	n.s.
Intracellular water	1043 ± 139 (−8)	1005 ± 75 (−8)	n.s.
Extracellular water	632 ± 58 (−24)	730 ± 71 (−22)	n.s.
Interstitial water	549 ± 57 (−26)	637 ± 67 (−24)	n.s.
Plasma volume	94 ± 8 (−1)	88 ± 4 (−3)	n.s.

Values are mean ± s.d. expressed as millilitres of water; OJ6, jaundiced, assessed 6 days after bile duct ligation; OJ12, jaundiced, assessed 12 days after bile duct ligation; numbers in parentheses express the mean percentage decrease of each compartment in respect to its preoperative value; n.s., not significant (Mann–Whitney *U* test) lower in jaundiced than in sham operated rabbits. Furthermore, the magnitude of the body weight reduction and the fall of creatinine clearance characteristic of jaundiced animals, were mimicked in a group of sham operated rabbits offered the same amount of water as that drunk by animals after bile duct ligation. Furthermore, body composition in sham operated water-restricted controls showed the alterations observed in obstructive jaundice. This suggests that reduced water intake plays an important part in the pathogenesis of contraction of the extracellular fluid compartment.

In this setting of extracellular fluid depletion associated with marginal hypovolaemia, factors such as endotoxin, aminoglycosides, haemorrhage or hypotension of any origin may easily lead to acute renal failure. Probably there are no specific mechanisms linking jaundice and renal failure but common, well known causes of renal failure can precipitate this complication much more easily in jaundiced patients because they are previously water depleted.

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Debridement and closed cavity irrigation for the treatment of pancreatic necrosis

M. Larvin,
A. G. Chalmers*,
P. J. Robinson† and
M. J. McMahon

*University Department of Surgery and *Department of Diagnostic Radiology, The General Infirmary, and †Department of Diagnostic Imaging, St. James's University Hospital, Leeds, UK*

Correspondence to:
Mr M. J. McMahon, University Department of Surgery, The General Infirmary, Leeds LS1 3EX, UK

Pancreatic and peripancreatic debridement combined with a closed cavity system of drainage was used to manage necrotic sequelae of severe acute pancreatitis in 14 patients. Intravenous contrast-enhanced computed tomography, or latterly incremental dynamic computed tomographic angiography, accurately detected and localized necrotic tissue. Operation was delayed where possible to permit demarcation of the necrotic area and the development of a 'capsule' of inflammatory tissue. A retrocolic route of access to the necrotic area was used in nine cases, and purpose-made silicone elastomer tubes with an outside diameter of 20 mm were positioned so that drainage was assisted by gravity when the patient was supine. The cavity was irrigated with saline (initially 2 litres daily), and in the last seven patients Trasylol® was included in the irrigation fluid (5×10^6 kallidinogenase inactivator (KI) units/litre) for the first postoperative week. Three elderly patients died (mean age 72 years) but all patients aged less than 68 years survived. Planned reoperation was carried out in two patients, but further reoperations were not required in the remaining 11. Drainage tubes were removed when contrast studies showed the cavity to be small and superficial; the median duration of drainage was 28 days. Although sinograms demonstrated fistulae between cavity and small bowel (n = 4) or small bowel and colon (n = 2), no clinical problems resulted and all closed spontaneously. Closed drainage may be as effective as techniques of marsupialization, but avoids the need for frequent relaparotomy.

Keywords: Acute pancreatitis, pancreatic necrosis, debridement, surgical drainage

Despite improvements in the management of critically ill patients, the overall mortality rate from acute pancreatitis in the UK remains about 10 per cent[1], although most attacks have a benign course and result in uncomplicated recovery. Serious complications of acute pancreatitis are frequently a consequence of necrosis of parts of the gland or adjacent tissues. Consequences of necrosis include pseudocysts in which the dominant lesion is a local collection of pancreatic juice, often producing relatively few symptoms, and abscesses in which an infected collection develops. In many of the most severely ill patients, extensive areas of the pancreas and/or peripancreatic tissues become necrotic, with a relatively small fluid component but with widespread oedema of adjacent tissues and organs. Infection complicates about half of the necrotic lesions[2,3]. Patients with extensive necrosis characteristically display clinical evidence of severe sepsis with rapid weight loss. Death usually results from multiorgan failure, days or weeks after the commencement of the attack of acute pancreatitis. Necrosis of the pancreas is present in the majority of patients who die from acute pancreatitis[1,4], hence it is probable that significant improvements in survival from severe acute pancreatitis will be achieved only when appropriate medical treatment is combined with efficient removal of necrotic tissue.

A policy of resectional surgery during the initial days of the attack appears to confer little benefit for survival and may actually increase the risk of mortality, even when confined to patients who remain severely ill despite intensive conservative management[5–7]. Pancreatic resection is a formidable undertaking in an ill patient, and the surgeon is a poor judge of what should be removed and what remains viable[7,8]. Bleeding may be severe both during and after the operation[9] and reoperation is commonly required to remove further accumulated necrotic tissue or to resect ischaemic bowel[10,11]. Patients with acute pancreatitis are highly 'catabolic'[12,13] and death from sepsis is a common sequel to resection[9,10].

An alternative to resection is debridement of the necrotic tissue, often termed necrosectomy or sequestrectomy[14], a procedure described by Moynihan in 1925[15]. A prerequisite to the removal of necrotic tissue is its accurate identification and localization. This has been facilitated by the introduction of computed tomography (CT) combined with intravenous contrast enhancement[16,17]. The operation itself is made easier and the postoperative course smoother if there is a clear plane of demarcation between necrotic and viable tissue, and if granulation tissue has formed, at least partly, in the walls of the cavity containing the necrotic tissue. Thus a 'maturation interval' between the onset of acute pancreatitis and debridement is desirable, but may not be feasible owing to increasing sepsis. Intravenous nutrition enables conservative management to be continued with less danger of progressive nutritional deterioration and without stimulation of enzyme release from the gland.

Recurrent necrosis and sepsis continue to be a problem in many patients after initial removal of necrotic tissue[9,10,18], and traditional methods of drainage, including sump drainage systems, appear to be inadequate to prevent it[19–28]. The fluid that escapes from the drains after pancreatic debridement contains high concentrations of enzymes, which probably ooze from disrupted ductal branches in the wall of the necrotic cavity after debridement. It is probably the continuing release of the enzymes, rapidly activated by necrotic tissue or blood, that causes further digestion and necrosis. The need for secretions

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Table 1 *Preoperative details of 14 patients with pancreatic necrosis*

Case	Sex	Age (years)	Identified cause of attack	Ranson score*	Imrie score*	Preoperative scores		Non-enhancing areas on CT	Extrapancreatic extension on CT	Day of debridement	Reason for operation
						APACHE-II	MRC				
1	M	50	Idiopathic	3+	2+	17	16	CT unavailable	—	39	Peritonitis
2	F	77	Gallstones	6	5	30	18	Head, body, tail	Caudal retro-peritoneum	21	Sepsis
3	M	59	Idiopathic	5	2	13	10	Head, body, tail	None	32	Sepsis
4	M	40	Alcohol	5	4	9	10	Head, body, tail	None	61	Sepsis
5	M	71	Gallstones	4	3	18	21	CT unavailable	—	37	Sepsis
6	M	58	Pancreatic carcinoma	5	4	18	16	CT unavailable	—	44	Peritonitis
7	M	40	Alcohol	5+	3+	7	11	Body and tail	Left anterior pararenal	96	Sepsis
8	M	40	Idiopathic	4	3	7	9	Body and tail	None	35	Sepsis
9	F	17	Gallstones	5	2	8	15	Head	Right anterior subhepatic space	30	Sepsis
10	F	60	Gallstones	4+	3+	13	15	Head, body, tail	None	17	Sepsis
11	M	36	Postoperative	4	2	17	17	Tail†	None	58	Sepsis
12	M	68	Gallstones	8	5	38	31	Head, body, tail†	Root of mesocolon	15	Sepsis
13	M	32	Alcohol	6+	3+	20	16	Body and tail†	None	10	Sepsis
14	M	64	Trauma	6	4	18	16	Head†	None	18	Sepsis

MRC, Medical Research Council; CT, computed tomography; * plasma lactate dehydrogenase was not available for calculation of Ranson and Imrie scores; † dynamic angiographic CT was employed

to flow against gravity when the patient is supine, along drains inserted through the anterior abdominal wall, and blockage of the drains by necrotic debris may be contributing factors to the genesis of postoperative sepsis.

Dissatisfaction with existing techniques of drainage has been an incentive to solving the problem of continuing intra-abdominal autodigestion. Repeated debridement or 'open' packing, a reintroduction of the practice first described in 1882 by Rosenbach, has been reported to lower mortality rates to 20–40 per cent[11,29–31], but recovery is usually prolonged, with substantial morbidity. However, it is perhaps the implementation rather than the concept of closed drainage that has been inadequate. Specific properties of a drainage tube for use after pancreatic debridement might include:

1. A diameter large enough to allow egress of necrotic tissue fragments
2. An irrigating channel to dilute and flush away enzyme-rich exudate and to prevent blockage of the drain
3. Sufficient rigidity to prevent distortion and collapse of the drain as it traverses the abdominal wall, but with non-traumatic properties so that erosion of vital structures such as vessels and loops of bowel is minimized
4. Adjustability, so that it can be repositioned easily as the cavity shrinks
5. The drain should be sited so that gravity assists rather than hinders drainage when the patient is supine
6. A closed drainage system is preferable to reduce the risk of infection and of digestion of the skin around the entry site.

In this report, a technique of closed drainage is described in patients who developed pancreatic necrosis after acute pancreatitis.

Patients and methods

Fourteen patients with pancreatic or peripancreatic necrosis underwent debridement and were treated using a dedicated closed drainage system. The age range of patients was from 17 to 77 years (median 54 years), and there were 11 men and three women (*Table 1*). Gallstones were identified in five patients, alcohol abuse in three and a pancreatic neoplasm in one case; one patient developed acute postoperative pancreatitis, and blunt trauma led to acute pancreatitis in one patient. The Ranson scores[32] (median 5) and Imrie scores[33] (median 3) confirm the initial severity of the attacks. Five of the patients were referred from other hospitals.

Each patient developed pancreatic necrosis, which was defined as the presence of one or more areas of necrotic pancreatic and peripancreatic tissue greater than 5 cm in diameter. Patients in whom collections of fluid or pus were the dominant element (*Figure 1a*), rather than solid necrotic tissue (*Figure 1b*), were not included as they were generally treated by internal drainage methods or guided percutaneous aspiration. Intravenous nutrition without oral food intake was instituted within 10 days of admission when it became clear that an early return to normal diet was not possible or that a pancreatic collection was probable.

Although pancreatic necrosis was suspected clinically, CT was most accurate, confirming the diagnosis and localizing the necrotic tissue, in 11 patients (*Table 1*). Three patients were treated before CT was routinely available at the General Infirmary. The diagnosis was confirmed at laparotomy in two patients, and in one case ultrasound scanning demonstrated a pancreatic collection within which solid necrotic tissue was visualized.

Before April 1986, CT was performed in seven patients using a Tomoscan 300, 310 or 350 scanner (Philips Medical Systems Ltd., London, UK). Upper abdominal scans were obtained after oral or nasogastric administration of 500 ml of a 3 per cent solution of Gastrografin® (10 per cent sodium diatrizoate, 66 per cent meglumine diatrizoate; Schering Pharmaceuticals, Burgess Hill, UK). Images of 12-mm thickness were obtained through the upper abdomen, and the pancreas was targeted. A rapid sequence of 6-mm thickness scans through the pancreas was carried out, at 15-s intervals, immediately after intravenous injection of concentrated contrast medium (50–100 ml of either 65 per cent meglumine diatrizoate (Urografin 310M®, Schering Pharmaceuticals) or 65 per cent iohexol (Omnipaque 300®, Nycomed (UK) Ltd., Birmingham, UK). In the four most recent cases, intravenous contrast CT angiography was performed[16,17] using a CT9800 scanner with a dynamic imaging facility (IGE Medical Systems Ltd., Slough, UK). Oral contrast medium was administered as before and 10-mm thickness scans were obtained. Non-ionic contrast medium (76 per cent iopamidol, Niopam 370®, E. Merck Ltd., Alton, UK) in a dose of 1·5–2 ml/kg body-weight (0·55–0·75 g iodine/kg) was injected as a rapid intravenous bolus, and a series of 10–12 incremental scans of 5-mm thickness were obtained dynamically through the entire pancreatic area (scan time 2 s, cycle time 8 s; *Figure 2*). Contrast enhancement values below 30 Hounsfield units were considered indicative of pancreatic necrosis[16].

The aim of management was to wait for at least 1 month, if possible, before proceeding to debridement, to enable the necrotic tissue to separate and the cavity to develop a well-defined wall. In five cases an operation was performed at an earlier stage when it became clear that sepsis was becoming life threatening despite intravenous nutrition and antibiotics (*Table 1*). In nine cases, it was possible to delay operation by more than 4 weeks, but evidence of continuing sepsis was present at the time of operation; in five of these patients sepsis was sufficiently severe for the operation to be carried out urgently, while in two of them emergency laparotomy was performed because a complication developed. In the 48 h before operation the range of peak leucocyte count was 8·2–47·1 × 10^9/litre (median 17·5) and the peak temperature range was 37·4–40·4°C (median 39·4°C). Preoperative Medical Research Council (MRC) sepsis scores[34] were in the range 9–31 (median 16) while APACHE-II scores[35] ranged from 7 to 38 (median 17, *Table 1*).

A midline incision was made in the first three patients and in two other patients who had a midline scar from a previous laparotomy. In nine cases, a bilateral subcostal incision ('rooftop' or 'chevron' incision) was employed. In nine patients, access to the necrotic cavity was gained by lifting up the transverse colon and applying digital pressure through the weakened and oedematous tissues at the root of the mesocolon in the vicinity of the duodenojejunal flexure. It was then possible to explore the cavity and its ramifications digitally, removing the necrotic tissue. Samples of necrotic tissue were sent for histological examination, immediate Gram staining, and aerobic and anaerobic culture. In one patient, who underwent operation on the tenth day of the attack (case 13), the necrotic pancreas was insufficiently friable for digital debridement, and sharp dissection was needed to transect it.

A specially designed drain made from silicone elastomer tubing with an outside diameter of 20 mm is shown in *Figure 3*. In the original hand-made version, a cuff of thin silicone elastomer sheet was bonded to the internal end (*Figure 3*) to prevent trauma to vessels and neighbouring viscera. An irrigating tube inside the main channel is brought out through the side wall, making this a closed system, and this tube accepts a standard male Luer connector. The drainage tubes are now manufactured with the cuff incorporated into the moulding (*Figure 3*) (Fehling Medizintechnik GmbH, Karlstein, FRG) and can be obtained from Medical Bionics, PO Box 63, Wokingham, UK. The drains were inserted into the cavity, from which the necrotic tissue had been removed, by two principal routes. By pushing a finger through the weakest point in the tail of the pancreas, a drain could be drawn into the central cavity using a long pair of artery forceps passed through

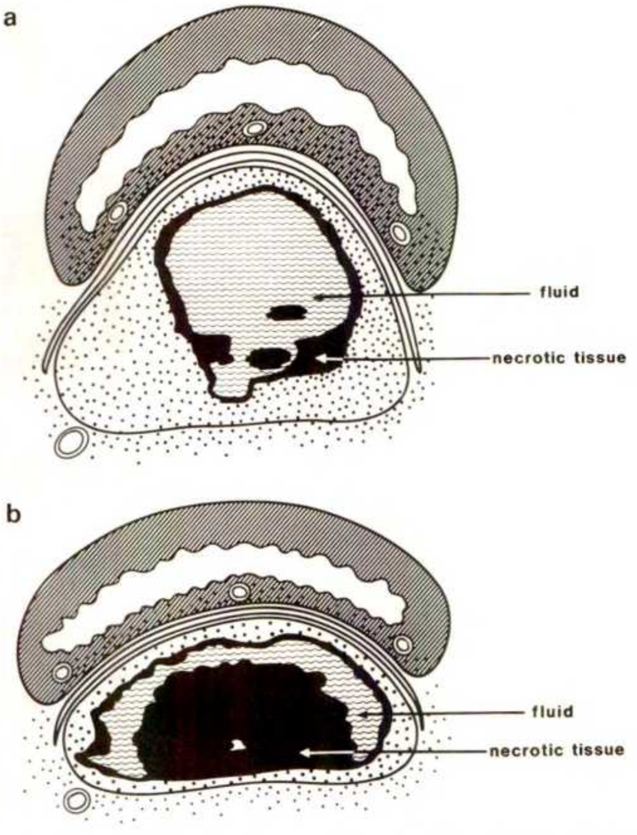

Figure 1 *Diagrams of* **a** *pancreatic abscess, an encapsulated collection of frank pus containing bacterial organisms, but only a relatively small amount of necrotic tissue, and* **b** *pancreatic necrosis in which necrotic tissue is the dominant element and may be surrounded by small amounts of pus. When mature, a capsule of inflammatory tissue is present*

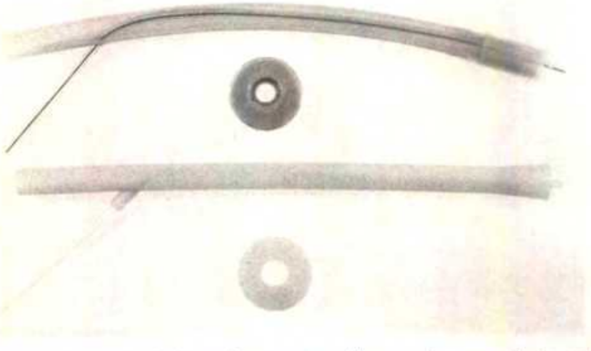

Figure 3 *Specially fashioned irrigating silicone elastomer drain and securing flange. Original version shown above; current manufactured version below*

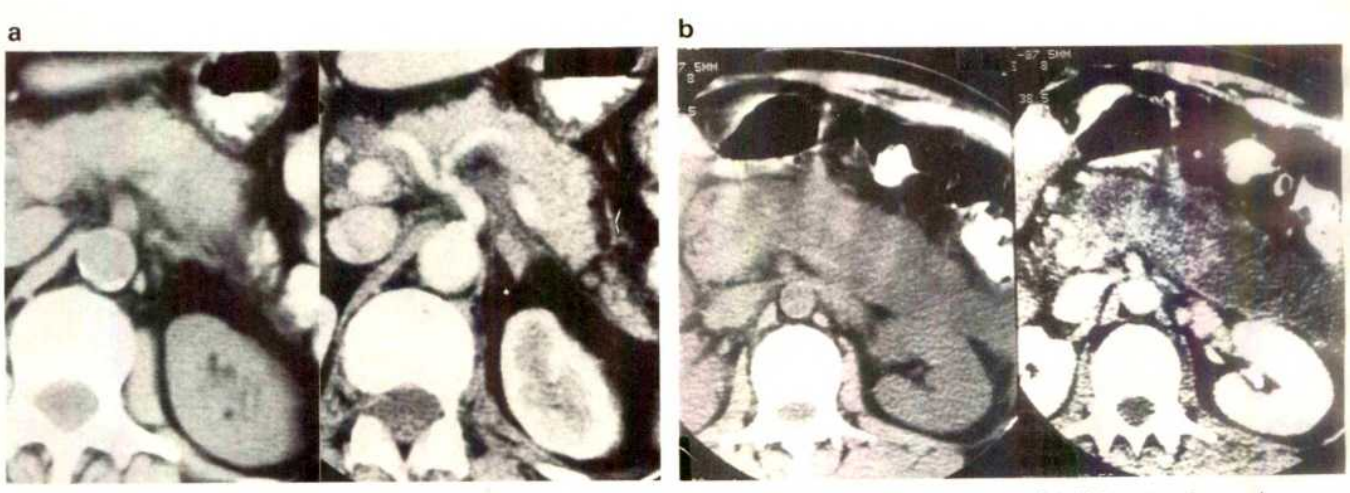

Figure 2 *Intravenous contrast computed tomography (CT) angiography:* **a** *precontrast (left) and postcontrast (right) CT images of normal pancreas demonstrating normal contrast enhancement. Note contrast in coeliac axis and major vessels;* **b** *precontrast (left) and postcontrast (right) images obtained in case 13. Note pancreatic swelling. Pancreatic tail and body enhance poorly, while enhancement of head is patchy*

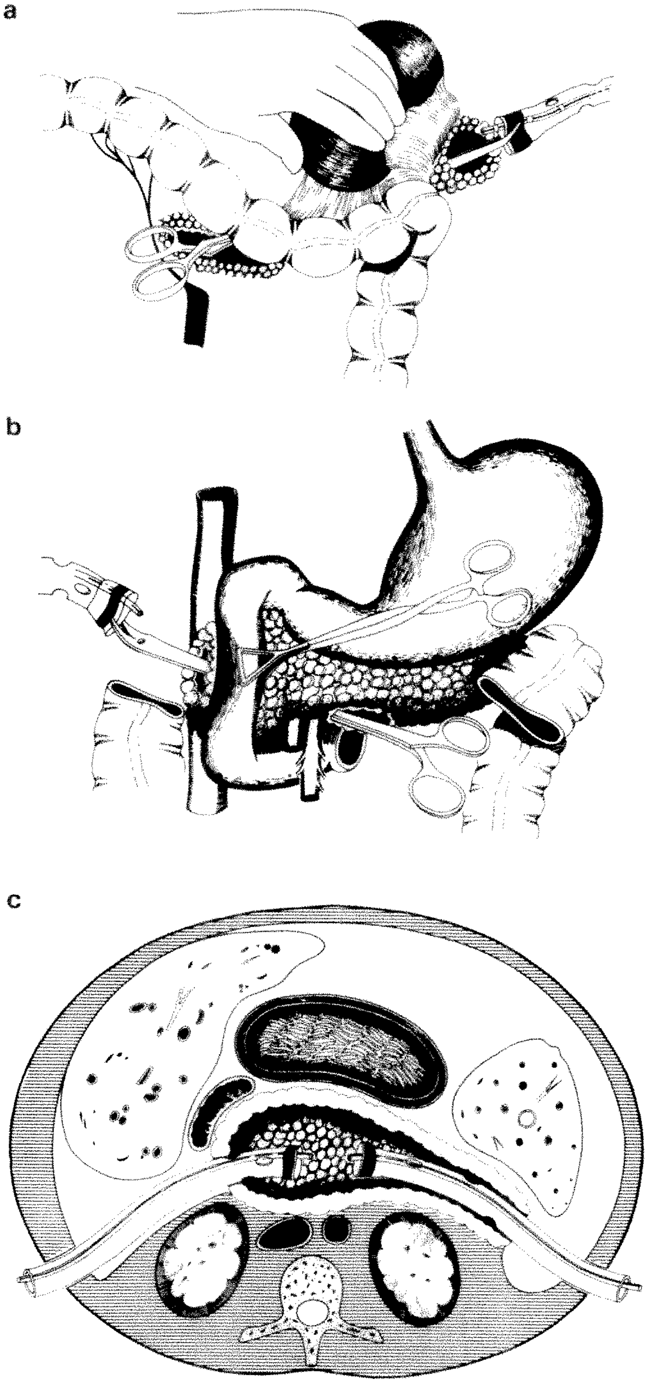

Figure 4 *Special drains:* **a** *insertion via tail of pancreas;* **b** *insertion via head of pancreas;* **c** *transverse section of drains* in situ. *Side holes were fashioned as shown if the cavity was extensive*

the access point in the transverse mesocolon (*Figure 4a*). Similarly, if there was cavitation in the head of the pancreas, a drain was introduced retroduodenally after Kocherization (*Figure 4b*). In five patients, drains were placed through the head and tail of the gland, and in nine patients a single drain was used (three via head, six via tail). In three patients, a small subsidiary silicone elastomer tube drain (7-mm diameter, Easyview®, Dow Corning Ltd., Reading, UK) was inserted through the access point in the transverse mesocolon. After insertion of the drains, the mesocolic access point was closed with silk sutures in order to isolate the cavity from the greater sac, and in two instances packs of non-adherent, soft paraffin-impregnated gauze (Jelonet®, Smith and Nephew Ltd., Hull, UK) were inserted in the proximity of the debrided area to ensure haemostasis. These were removed at re-laparotomy the next day. The drains were brought out through the abdominal wall as posteriorly as possible in order to ensure dependent drainage (*Figure 4c*). If the cavity was large and the drains extended for some distance within it, small side holes were fashioned. Flanges made from silicone elastomer were used to anchor the drain to the skin (*Figure 3*). The drain was pulled through the central hole in the flange, which was attached to the skin using three or four silk sutures. The drain was a sufficiently tight fit within the flange that dislodgement did not occur.

The debrided cavity was irrigated with 2 litres of saline per day, administered as an hourly bolus in order to 'flush' the cavity. When the return fluid was clear, usually after 7–10 days, the volume was reduced to 1 litre daily. Recently we have added an antiprotease, Trasylol® (Bayer UK Ltd., Newbury, Berks, UK), at a concentration of 1×10^6 kallidinogenase inactivator (KI) units in each litre of saline (seven patients). A sinogram was carried out weekly by injecting radio-opaque contrast medium (25–40 per cent sodium diatrizoate, Hypaque 25® and Hypaque 40®, Sterling Research Laboratories, Guildford, UK) via the irrigation channel. This enabled the position of the drain to be adjusted so that there was free drainage of the cavity. Drains were removed when the cavity closed.

Results

The extent of necrosis, results of bacteriological investigations, and other data are shown for each patient in *Table 2*. Extensions of the necrotic cavity beyond the confines of the pancreas were present in five cases. The wet weight of specimens varied from 30 to 160 g (median 90 g). The median period of irrigation after operation was 19 days. The median amylase concentration from the irrigated drains of six patients during the first week after debridement was 48 000 units/litre. We did not determine protease concentrations independently but would expect levels to be similarly elevated. In addition, the drainage fluid was characteristically 'prune juice' coloured, suggesting continuing digestion. Under these circumstances, inclusion of an antiprotease seemed logical. After Trasylol was added to the irrigating fluid, the dark colour of the drainage fluid disappeared within 48 h.

Bleeding into the drain occurred in one case, but this resolved spontaneously. Infection complicated all of the midline wounds but none of the transverse incisions. Fistulae between the cavity and bowel were revealed at sinography in six patients. In four cases the cavity communicated with jejunum, and in two cases with both jejunum and colon. In two cases, a communication with the pancreatic duct was observed. However, there was no clinical evidence of fistula formation and specific treatment was not required; all fistulae closed spontaneously. The drains were removed, under radiographic control, between 13 and 41 days after debridement (median 30 days in survivors). Intravenous nutrition was discontinued when the patient was able to return to a normal diet and major discharge from the drain site had ceased. The median duration of intravenous nutrition was 37 days (range 11–98 days). Patients were discharged from hospital 26–140 days after operation (median 44 days). No patient developed colonic ischaemia.

Three patients died. One was a woman of 77 years, with overwhelming sepsis at the time of operation and established respiratory, cardiovascular and renal failure. Debridement, which was performed 21 days after admission, did not appear to influence the course of her illness. She died 6 days postoperatively and autopsy revealed gross pulmonary oedema. A 71-year-old man died 50 days after operation from the complications of a small bowel fistula not directly related to the pancreas but caused while gaining access to the abdomen. He had suffered a shrapnel injury during World War II and there were dense adhesions throughout the abdomen. A man of 68 years, with severe chronic respiratory disease, angina and hypertension, who had established renal failure at the time of admission to hospital, developed intractable multiorgan failure and coagulopathy. By computed tomographic angiography with guided needle aspiration, it was shown that he had infected peripancreatic necrosis. Debridement was carried out on the 15th day of the attack, but did not influence the multiorgan failure, and he died 4 days later.

The 11 survivors were followed for periods from 8 months to 7 years. Three were diabetic; in two cases only dietary

Table 2. *Postoperative details of patients*

Case	Location of pancreatic necrosis	Extrapancreatic extension	Bacterial organisms cultured	Sites of insertion of drainage tubes	Irrigation period (days)†	Drainage period (days)†	Outcome
1	Head, body, tail	Caudal retroperitoneum	Mixed enteric flora	Head and tail	15	33	Discharged, day 179
2	Head and body	Caudal retroperitoneum	Coliforms	Head	(6)	(6)	Died, day 27
3	Head, body, tail	None	β-haemolytic streptococci; *Staphylococcus aureus*	Head and tail	19	28	Discharged, day 76
4	Head, body, tail	None	Mixed enteric flora	Head and tail	18	28	Discharged, day 100
5	Head, body, tail	None	No organism cultured	Head and tail	12	26	Died, day 87
6	Body and tail	None	No organism cultured	Tail	24	31	Discharged, day 110
7	Body and tail	Left transverse mesocolon	Coliforms; β-haemolytic streptococci	Tail*	27	27	Discharged, day 137
8	Body and tail	None	*S. aureus*	Tail*	23	24	Discharged, day 87
9	Head	Right anterior subhepatic space	Coliforms; *Bacillus proteus*	Head	12	13	Discharged, day 56
10	Head, body, tail	None	*S. aureus*	Tail*	31	34	Discharged, day 66
11	Tail	None	*S. aureus*; coliforms	Tail	34	41	Discharged, day 102
12	Head, body, tail	Transverse mesocolon	Mixed enteric flora	Head and tail	(4)	(4)	Died, day 19
13	Body and tail	None	No organism cultured	Tail	23	33	Discharged, day 48
14	Head	None	Coliforms	Head	20	32	Discharged, day 68

* Subsidiary 7-mm outside diameter silicone elastomer tube drain was also employed. † Parentheses indicate deaths that occurred with drains *in situ*

treatment was required, while one patient required insulin therapy. None of the patients complained of steatorrhoea. All remain well, with the exception of one patient who subsequently died from a disseminated carcinoma of the head of the pancreas, probably the cause of his attack of acute pancreatitis but which was unrecognized at the time of debridement.

Discussion

In this report we have used the terms pancreatic necrosis and peripancreatic necrosis to mean an extensive area of the pancreas or peripancreatic tissue which was necrotic although, inevitably, pus, fibrin and blood were also present. In each case necrosis occurred as a consequence of acute pancreatitis and resulted in a severe, 'septic' illness characterized by pyrexia and leucocytosis, although organisms were cultured from only 11 samples of necrotic tissue (79 per cent), and blood cultures were negative. The term pancreatic abscess has also been used to describe similar lesions in the pancreas, but we feel it is more appropriate to use it if pus is the major component rather than necrotic tissue. The weight of necrotic tissue removed ranged from 30 to 160 g, and tissue was principally peripancreatic in one patient.

The management of pancreatic necrosis has become more precise with the development of CT, particularly with the use of intravenous contrast enhancement[16,17,30]. Ultrasound is of little value for the identification of necrotic tissue[17,36]; the clinical evaluation of the patient is unreliable, and the surgeon's ability to distinguish viable from necrotic tissue has been found wanting[7,8,37]. The use of high-dose intravenous contrast enhancement (0·55–0·75 g iodine/kg body-weight) and dynamic scanning improves the precision of CT[17,30] and enables a more accurate delineation of pancreatic from peripancreatic necrosis. Notwithstanding their value, CT appearances alone are inadequate as an indication of the need to intervene surgically, and other patients we have treated have shown gradual improvement and eventual resolution of sepsis, despite equivocally abnormal CT contrast enhancement. Thus our policy has been to continue conservative management until the need for operation becomes imperative on clinical grounds, using CT to monitor the progress of changes in the pancreas. When operation was undertaken, however, CT provided a most valuable guide to the location and extent of necrotic tissue. The timing of operative intervention is probably important. Operations carried out during the initial days of the attack are frequently fatal[5,9], and delay to permit diagnostic investigations and to allow clear demarcation of the necrotic tissue appear warranted. Nevetheless, it is important to operate before multiorgan failure has become established, or the mortality rate is also likely to be high[10,38]. The patient who becomes severely ill with a necrotic pancreas during the initial days of the attack places the surgeon on the horns of a dilemma. Certainly, a trial of continued conservative management incorporating intravenous nutrition, even in the presence of very severe sepsis, appears justified because in our experience complete resolution may occur. At laparotomy, oedema of the peripancreatic tissues and thickening of the omentum and mesocolon make assessment of the pancreas difficult.

Access to the necrotic area through the root of the transverse mesocolon, also recently advocated by others[37,39], was found to be simple and convenient in nine of the patients. While such access does not permit the thorough examination of the pancreas and posterior abdominal wall that can be obtained by extensive division of the gastrocolic omentum, it entails considerably less trauma and blood loss. Moreover, the more traditional gastrocolic approach breaks down the 'capsule' that forms around the necrotic material, and thus allows pancreatic juice to disseminate widely in the upper abdomen postoperatively and to contribute to continuing necrosis. The approach via the transverse mesocolon can be closed easily after the insertion of drainage tubes and thus permits closed cavity irrigation to be carried out.

The need for irrigation is controversial. It has been strongly recommended by some authors[38,40–42] but others have used multiple, soft, tubular drains without irrigation[39] and have achieved apparently comparable results. We have used irrigation as a logical method of scavenging the cavity, and to prevent the accumulation of erosive pancreatic juice. In the first postoperative week, the effluent from the drainage tube has the appearance of the 'prune juice' fluid that accumulates within the peritoneal cavity during severe acute pancreatitis. Combined with high levels of pancreatic enzymes, the appearance suggests that enzymes are activated locally (by necrotic tissue, leucocyte enzymes or blood) with resultant autodigestion. For this reason we added aprotinin (Trasylol) to the irrigation fluid for the seven most recent patients, and it appeared that the colour of the fluid resolved more rapidly. A closed system was employed to prevent ingress of infection, and appears to have achieved its aim.

There was a high incidence of bowel fistulae, as visualized on the postoperative sinograms. Nevertheless clinical problems were not identified with fistulae and there was no drainage of intestinal fluid via the drains. All would have gone unnoticed if frequent sinograms had not been obtained. We believe that regular sinograms were justified, because in four patients it was found that the cavity had contracted so that drainage became inefficient.

The use of gauze packs[29–31] and frequent relaparotomy[11], which has become fashionable recently, is an alternative method to remove the erosive juice that exudes from the cavity after debridement, the pack acting as a sponge. We favour the concept of closed cavity irrigation, but careful design and placement of the drainage tubes is probably crucial to success. The features that have been incorporated into the system described (wide bore, atraumatic, resistant to collapse, irrigating facility, adjustability and gravity-assisted drainage) make it as different from traditional drainage tubes as open packing. Recent studies of carefully carried out drainage appear to be as successful as open packing techniques from the standpoint of mortality[39,41], and reoperation was not a frequent requirement.

In the present study, three of 14 patients died (21 per cent), but all were aged over 65 years and the youngest of them was already chronically ill with established multiorgan failure at the time of admission with acute pancreatitis. Survival from pancreatic necrosis is less common in patients aged 60 years or more[43] and, in our opinion, it is unlikely that the open packing technique would have secured survival in the patients who died. A randomized study may be necessary to decide the issue—a daunting prospect.

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Open abdomen technique in the treatment of peritonitis

V. I. Korepanov

Hospital of Moscow Building Industry, Moscow, USSR
Correspondence to:
Dr V. I. Korepanov, Academica Millionshikov Street 35,
Block 2, Apartment 13, 115446 Moscow, USSR

To stimulate the interest of Russian surgeons in the open technique for the treatment of peritonitis, I recently reviewed the reports of foreign investigators[1,2]. All such authors refer to Steinberg[3,4], who has been acknowledged as a pioneer of the method. I do not wish to detract in the slightest from the outstanding role of Steinberg in developing this new technique, however, it should be noted that the method had grown from the Mikulicz technique elaborated at the end of the last century. This method was modified slightly by the French surgeon Faure[5] who used it to treat pelvic abscesses and peritonitis in women. Faure prepared a sac from multilayered gauze and placed it deep into the pelvis; long narrow gauze tampons were put into the sac to fill the pelvic cavity. The author left the abdominal cavity open for 9–10 days, but beginning on the third day he removed from two to four tampons a day, completing withdrawal by the ninth or tenth day. The final stage consisted of closure of the abdomen. A similar technique of abdominal tamponage was used by Anderson *et al.*[6] who packed the lateral spaces of the abdominal cavity, covering the viscera with a gauze pack. Unfortunately, the results were discouraging, the mortality rate reaching 60 per cent.

Steinberg[3] proposed a more gentle approach leaving the abdominal cavity open with the viscera covered by a large gauze pack for not more than 72 h. As a result only one patient died of the 14 (7 per cent) so treated. For severe peritonitis he recommended that the pack should be kept in position for up to 10 days because more frequent changes could cause intestinal fistula formation[4]. Using this technique 17 per cent of patients died.

In 1984 the Russian surgeon Makhocha[7] reviewed his personal experience with the open abdomen technique in 128 patients suffering from severe peritonitis, 106 of whom survived (83 per cent). He referred to his first communication dated 1967 and based on his originally elaborated technique which had been applied as early as 1949[8]. This report was published in Russian in the *Proceedings of the Ukraine Scientific Surgery Society* in Kiev and remained unknown not only to foreign surgeons but also to Russian surgical circles. A translation of that article is as follows:

> The source of peritonitis is eliminated and the abdominal cavity dried but not lavaged. A large (40 × 40 cm) two-layer gauze napkin is sutured in the centre by a strong silk ligature. This napkin covers the viscera, its borders overlapping the wound edges by 5–6 cm. The ligature is pulled up and the space in the centre of the napkin is filled with from four to eight gauze tampons, the ends of which are located outside the wound. Alongside the tampons catheters are put into the abdominal cavity for instillation of antibiotics. Two all-layer sutures are placed through both the upper and lower angles of the midline abdominal wound. The integral parts of a dressing are fixed in position with the help of a large long towel wrapped tightly around the patient's body. In the postoperative period the superficial layers of the dressing are changed as soon as they become wet. Tampons are gradually withdrawn starting from the fourth day; this procedure is completed by the 10th to 15th day. Then the napkin is pulled out, using the silk ligature, step by step and removed by the 18th to 21st day.

In the initial study of 26 patients all but four survived (85 per cent), excellent results when taking into consideration the fact that five patients required an enterostomy. In his last article[7] the author advised changing the tampons every 2–3 days, leaving the napkin longer until body temperature and intestinal motility returned to normal.

Presently, we have available at least three articles by Russian surgeons published in the domestic medical literature[9–11] that deal with the open abdomen technique for advanced peritonitis with a 17 per cent mortality rate. This short report may alert foreign specialists in abdominal surgery to investigations conducted by Russian surgeons.

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Threshold for albumin as a prognostic marker in acute pancreatitis

M. P. Holliday, D. Shaw, W. M. Thomas* and T. Leese*

*Department of Chemical Pathology and *Department of Surgery, University of Leicester, Leicester, UK*

Correspondence to: Dr M. P. Holliday, Department of Chemical Pathology, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, UK

Several multifactor prognostic scoring systems for acute pancreatitis use serum albumin[1–3]. The prognostic threshold of 32 g/l derives from an assay using bromocresol green dye-binding reagent, calibrated against purified human serum albumin[4]. This method routinely over-estimates serum albumin when calibrated against a purified human serum albumin standard, which is common practice[5]. This positive error has a magnitude of 2–12 g/l and arises from interference by α- and β-globulins, which include some of the acute phase proteins[5–7]. Bromocresol purple reagent is specific for albumin[5,7]. More than 10 per cent of UK laboratories now use bromocresol purple routinely, as does the Abbott Vision analyser (Abbott Laboratories, Chicago, USA), an instrument conveniently used for albumin measurement on emergency samples[8].

The magnitude of the globulin error in acute pancreatitis has not previously been evaluated. This study was designed to determine the corresponding bromocresol purple–albumin threshold in an established bromocresol purple assay in routine use and in the Abbott Vision bromocresol purple method.

Patients and methods

Sixty-four patients (32 men) were recruited randomly from hospital admissions for acute pancreatitis in Leicestershire over 23 months. Serum was collected within 24 h of admission. The mean age was 58·3 years (range 17–87 years). Twenty-six cases were scored as prognostically severe on admission according to the Glasgow criteria[1]. Aetiologies and complications are shown in *Tables 1* and *2*. The albumin assays are outlined in the Appendix to this paper.

Results

Scatterplots of results from the established bromocresol purple and Abbott Vision bromocresol purple methods *versus* the bromocresol green method are shown in *Figures 1* and *2*. Regression parameters are summarized in *Table 3*. The regression equations by Deming's method (with 95 per cent confidence intervals for the slope) are:

Established bromocresol purple–albumin (g/l) = −5·11 + 1·02 (0·96 – 1·08) bromocresol green–albumin (g/l)

Abbott Vision bromocresol purple–albumin (g/l) = −4·88 + 1·04 (0·99 – 1·09) bromocresol green–albumin (g/l)

The standard *y*-on-*x* regression equations are:

Established bromocresol purple–albumin (g/l) = 0·50 + 0·87 bromocresol green–albumin (g/l)

Abbott Vision bromocresol purple–albumin (g/l) = −2·72 + 0·98 bromocresol green–albumin (g/l)

Bromocresol purple–albumin thresholds (with 95 per cent confidence intervals) predicted from the standard regression lines where bromocresol green–albumin = 32 g/l are:

Established bromocresol purple method 28·3 (27·6 – 29·1) g/l

Abbott Vision bromocresol purple method 28·7 (28·0 – 29·4) g/l

Table 1 *Aetiologies of acute pancreatitis in the 64 patients studied*

	No. of patients	%
Gallstones	32	50
Alcohol	16	25
Idiopathic	13	20
After ERCP	2	3
Pancreatic duct stricture	1	2

ERCP, endoscopic retrograde cholangiopancreatography

Table 2 *Complications of acute pancreatitis in the 64 patients studied*

	No. of patients	%
Deaths	6	9
Non-fatal complications*	9	14
No complications	49	77

* Pseudocyst, pancreatic abscess, ileus, gastrointestinal haemorrhage, pleural effusion, pneumonia, congestive cardiac failure

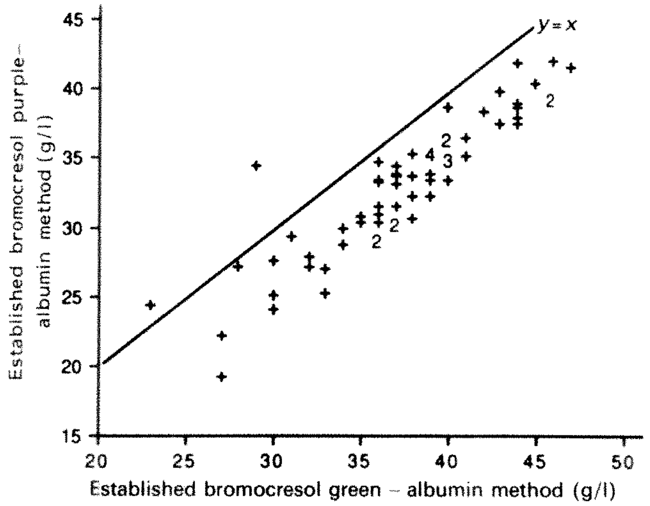

Figure 1 *Scatterplot of an established bromocresol purple–albumin method against an established bromocresol green–albumin method in acute pancreatitis sera*

Discussion

The Deming slopes do not differ significantly from unity at the 5 per cent level of probability. This is consistent with the presence of a constant bias in bromocresol purple–albumin results with respect to bromocresol green–albumin over the range studied. The magnitude of the bias, about −5 g/l, is similar to that reported in sera from other sources[7].

The accuracy of the bromocresol green assay used here approximates closely to the UK national average performance for this method as measured by the UK External Quality Assessment Scheme for General Clinical Chemistry (UKEQAS for General Clinical Chemistry, Wolfson Research Laboratories, Birmingham, UK). During the study bromocresol

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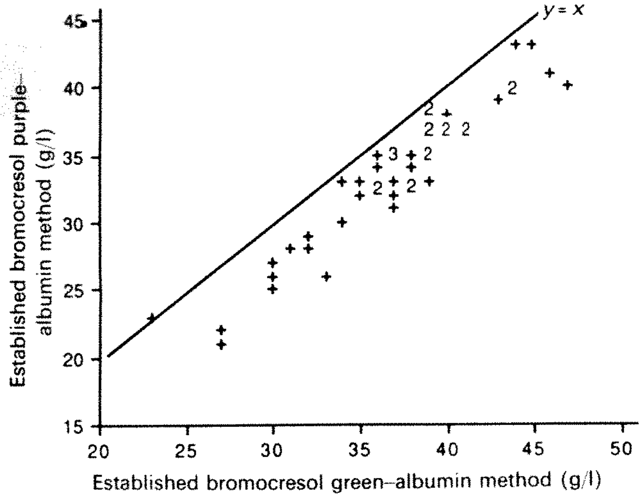

Figure 2 *Scatterplot of the Abbott Vision bromocresol purple–albumin method against an established bromocresol green–albumin method in acute pancreatitis sera*

green–albumin results from this laboratory carried an average bias of +0·8 per cent with respect to the national mean for continuous flow methods using succinate buffer ($n = 91$). Results were on average 2·0 per cent from this target value, which compares with a national interlaboratory coefficient of variation of about 4·0 per cent for this method.

Predicted bromocresol purple thresholds were 28·3 g/l from the established assay and 28·7 g/l from the Abbott Vision assay. It is recommended that where bromocresol purple is used the prognostic threshold be adjusted to 28 g/l, or to 28·5 g/l if results are reported to three significant figures or obtained from the Abbott Vision analyser.

The bromocresol purple method for albumin is gaining popularity and users of prognostic scoring systems in acute pancreatitis should be aware of the chemistry of their local method.

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Table 3 *Summary of regression parameters of the two bromocresol purple–albumin methods on bromocresol green–albumin*

y	Established bromocresol purple	Abbott Vision bromocresol purple
x	Bromocresol green	Bromocresol green
n	64	47
Mean *x*	37·48	37·00
Variance of *x*-data	26·98	25·96
Standard error of regression (S*y*.*x*)	2·047	1·666
Correlation coefficient	0·9121	0·9498
Slope	0·8697	0·9816
y-intercept	0·502	−2·723
Deming slope	1·019	1·040
Deming *y*-intercept	−5·109	−4·879
Deming S*y*.*x*	0·787	1·122

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Appendix I

Albumin assays

1. An established bromocresol green method[9] on a Technicon SMAC II (Technicon Instruments Corporation, New York, USA) continuous flow multichannel analyser (pH 4·2 succinate buffer, 60 s reaction time), using Technicon SMAC calibrators, themselves calibrated against a gravimetric Cohn fraction 5 human serum albumin standard using the same reagent[10]. The standard deviation of within-run analytical imprecision at 29 g/l was 0·51 g/l.

2. An established bromocresol purple method[11] on a discrete multichannel analyser (pH 5·5 0·1 M acetate buffer, 0·09 mmol/l bromocresol purple, ionic strength adjusted with sodium chloride to a final chloride concentration of 0·15 mol/l), using pooled human serum as calibration material, itself calibrated immunochemically against the Sheffield (UK) Protein Reference Unit standard SPS-01 (PRU Central Antiserum Purchasing Unit, Royal Hallamshire Hospital, Sheffield, UK). The standard deviation of within-run analytical imprecision at 25 g/l was 0·20 g/l.

3. The Abbott Vision bromocresol purple method (pH 5·4 0·125 mol/l acetate buffer, 0·19 mmol/l bromocresol purple), using calibrators supplied by the manufacturer. The standard deviation of within-run analytical imprecision at 36 g/l was 0·47 g/l.

Data analysis

The standard least-squares regression line of bromocresol purple–albumin results on bromocresol green–albumin was used to predict the corresponding bromocresol purple–albumin thresholds. Deming's least-squares regression formula, which takes account of analytical imprecision in the independent variable, was used to obtain estimates of the slope appropriate for the detection of proportional (concentration-dependent) bias[12,13]. Within each assay the standard deviation of analytical imprecision was assumed to be constant over the range of concentrations encountered.

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Mesoatrial shunt: a surgical option in the management of the Budd–Chiari syndrome

The Budd–Chiari syndrome, arising from hepatic venous outflow obstruction, is frequently complicated by inferior vena caval occlusion or obstruction. Satisfactory decompression of the liver by either portacaval or mesocaval shunts may therefore prove impossible or be prone to failure from shunt thrombosis. The mesoatrial shunt which allows the portal vein to drain directly into the right atrium has previously been advocated in this situation. Five patients with the Budd–Chiari syndrome and caval occlusion and/or obstruction have had mesoatrial shunts constructed using externally supported polytetrafluoroethylene grafts. A single thoracoabdominal incision, incorporating a median sternotomy, was found to provide a satisfactory approach. All patients recovered well with resolution of ascites, diminution in liver size and improvement in inferior vena caval pressure gradients. Furthermore, all shunts have remained patent, as determined by Dopper flow studies and contrast-enhanced computed tomographic scanning, during follow-up periods ranging from 9 to 16 months. If these results are supported by longer term studies, the mesoatrial shunt may become the surgical treatment of choice in patients with hepatic vein occlusion and the Budd–Chiari syndrome associated with inferior vena caval obstruction.

Keywords: Budd–Chiari syndrome, portosystemic shunts, portal hypertension, vena cava, obstruction

M. D. Stringer,
E. R. Howard,
D. W. Green*, J. Karani†,
A. S. Gimson‡ and
R. Williams‡

Departments of Surgery,
**Anaesthesia, †Radiology and the*
‡Liver Unit, King's College Hospital,
Denmark Hill, London SE5 9RS, UK
Correspondence to:
Mr M. D. Stringer

Hepatic venous outflow obstruction was originally reported by Budd in 1845[1] but the first description of the clinical syndrome of hepatomegaly, ascites and abdominal pain is attributed to Chiari in 1899[2]. The clinical features may follow inferior vena caval obstruction or hepatic vein thrombosis and/or obstruction. The syndrome also develops with central hepatic veno-occlusive disease[3]. These processes may reflect an underlying predisposition to venous thrombosis such as that, which occurs in overt or latent myeloproliferative disorders[4], paroxysmal nocturnal haemoglobinuria, pregnancy and in women using the oral contraceptive pill. Less common causes include inferior vena caval webs (particularly in Japan[5]), trauma and tumours (principally renal, adrenal and hepatocellular carcinomas).

The disease runs a variable clinical course ranging from an acute, rapidly fatal illness[6,7] to a more usual chronic condition characterized by progressive ascites and wasting and accompanied by cirrhosis and portal hypertension. Despite the very rare cases of spontaneous resolution[8], most patients have a poor prognosis with only 50 per cent surviving for 2 years[9]. With the increasing recognition of the limitations of medical therapy there has been a proliferation of reports describing surgical solutions to the syndrome. These have largely dealt with portosystemic shunting. In preparing patients for such operations, imaging studies of the inferior vena cava (IVC) have revealed a high incidence of obstruction or occlusion of the IVC[10–14], which seriously prejudices the patency of these shunts and thus their effectiveness in decompressing the congested liver. To avoid these difficulties, Cameron and Maddrey[15] described the mesoatrial shunt which allows the portal venous system to drain directly into the right atrium, bypassing the inferior venal caval obstruction.

We have constructed a mesoatrial shunt, with some technical operative modifications, in five patients with the Budd–Chiari syndrome and report our early results of clinical outcome and shunt patency.

Patients and methods

The patients in this series (four female, one male) ranged in age from 14 to 54 years and all presented with hepatomegaly, massive ascites and various degrees of malnutrition. A diagnosis of Budd–Chiari syndrome was confirmed by hepatic venography in all cases and by preoperative liver biopsy in three patients. The condition was associated with an underlying myeloproliferative disorder in four of the five cases. Investigations also included ultrasound and computed tomographic (CT) scanning, inferior vena cavography with pressure measurements from the right atrium and the infrahepatic cava (*Figure 1*), and mesenteric arterioportography which provided an assessment of the size and patency of vessels in the portal venous system[16,17]. Superior mesenteric vein diameters estimated radiologically were 12–13 mm. All five patients had evidence of obstruction or occlusion of the IVC (*Table 1*). The indications for surgery included: medically intractable ascites, deteriorating liver function with Rappaport zone 3 necrosis in the liver biopsy specimen, and progressive cachexia and wasting.

Patients were prepared for surgery by regular paracentesis (and thoracocentesis in one case), vitamin K, diuretics (spironolactone and frusemide) and 48 h of oral therapy with metronidazole, neomycin and lactulose. No specific haematological measures were undertaken, other than to discontinue anticoagulants in the two patients who were receiving these for myeloproliferative disorders.

After anaesthetic induction, monitoring catheters were inserted to record the following: arterial pressure and blood gases; pulmonary artery pressure, pulmonary capillary occlusion pressure and cardiac output; central venous pressure and urine output. Cardiac output was determined in all patients by a thermodilution technique utilizing a flow-directed pulmonary artery catheter. Measurements were made throughout the operative period and immediately before and after shunt opening. In two patients, cardiac output was measured continuously by Doppler or impedance techniques.

Operative details

After an initial laparotomy via a midline abdominal incision, the superior mesenteric vein was dissected free in the root of the small bowel mesentery. After proximodistal control, a 2–3-cm length of the vessel was isolated for the anastomosis. A median sternotomy was carried out in a synchronous combined manner and the pericardium

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was opened. The lateral wall of the right atrium was cross-clamped just below the auricle and 5000 units unfractionated heparin was given intravenously. A 13-mm spirally reinforced expanded polytetrafluoroethylene (PTFE) graft (Impraflex® Impra Incorporated, Arizona, USA) was sutured obliquely end-to-side to the superior mesenteric vein and to the right atrium with continuous 5/0 Prolene® (Ethicon Ltd., Edinburgh, UK). The graft follows an S shaped route from the atrium, through a subxiphoid V shaped incision in the diaphragm, around the left lobe of the liver passing anteriorly to the stomach and through the transverse mesocolon (*Figure 2*). Portal vein pressures were recorded before and after construction of the shunt. After haemostasis, the wounds were closed (but not the pericardium) with a pericardial drain and an abdominal wound drain.

The patient was electively ventilated for at least 24 h with close monitoring of cardiovascular, pulmonary, renal and haematological functions. Drains were removed within 72 h. Prophylactic antibiotics were continued until invasive monitoring lines were withdrawn and prophylactic H_2 antagonists and parenteral nutrition were continued until enteral feeding was re-established. Patients were commenced on subcutaneous low-dose heparin prophylaxis (5000 units twice daily) if and when the prothrombin time became less than twice normal.

Results

A satisfactory mesoatrial blood flow was established through the graft in each case with concomitant reduction in the portal venous pressure (*Table 1*). Creation of the shunt resulted in a dramatic rise in cardiac output in two patients (Nos. 2 and 3) from 4·5 to 6·8 litres/min and from 5·0 to 7·0 litres/min, respectively. A less marked increase in cardiac output (from 4·9 to 5·0 litres/min (No. 1), from 3·4 to 4·0 litres/min (No. 4) and from 3·9 to 4·0 litres/min (No. 5)) was observed in the other three patients. These results obtained by thermodilution were mirrored by the continuous measurements using Doppler impedance methods. We experienced no operative mortality although the postoperative course in patient No. 1 was complicated by hypotension and oliguria requiring inotropic support and basal pneumonia exacerbated by severe respiratory weakness secondary to malnutrition. Another patient (No. 3) developed postoperative bleeding from the pericardial drain (maximum 500 ml/h) which ceased after correcting his coagulopathy.

All patients subsequently made good recoveries with resolution of ascites and striking improvements in nutritional status and general well-being. Furthermore, all shunts have been demonstrated to be patent by means of Doppler ultrasound studies (reversed flow in the portal vein and turbulent flow in the shunt) and dynamic CT scanning (*Figure 3a* and *b*). CT scans have also revealed significant reductions in liver size with diminution of the caudate lobe in all patients. Doppler studies have indicated increased hepatic

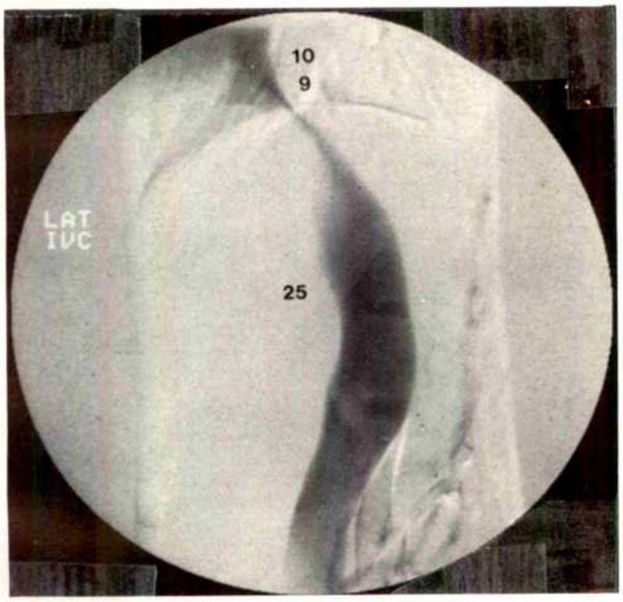

Figure 1 *Lateral view of inferior vena cavagram (patient No. 4) demonstrating caudate lobe compression. Pressures (mmHg) in the right atrium, suprahepatic inferior vena cava (IVC) and infrahepatic IVC are shown*

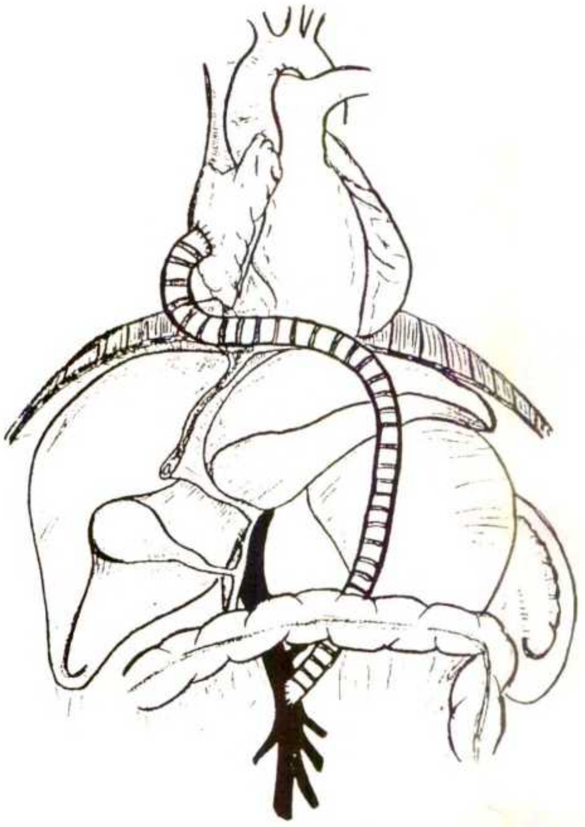

Figure 2 *Diagrammatic representation of the mesoatrial shunt*

Table 1 *Haemodynamic data in patients undergoing mesoatrial shunting for the Budd–Chiari syndrome*

Patient	Age (years)	Preoperative IVC gradient (mmHg)	Intraoperative portal vein pressure decrease (mmHg)	Postoperative stay (days)	Patency ± repeat IVC gradient (mmHg)	Follow-up (months)
1	33	Occluded IVC	30→15	42	Patent	16
2	46	17 (20→3)	31→15	15	Patent (4-mm gradient)	15
3	14	25 (25→0)	29→15	17	Patent (4–6-mm gradient)	15
4	25	16 (25→9)	38→16	22	Patent (2–4-mm gradient)	12
5	54	8 (17→9)	18→0	23	Patent	9

IVC, inferior vena cava

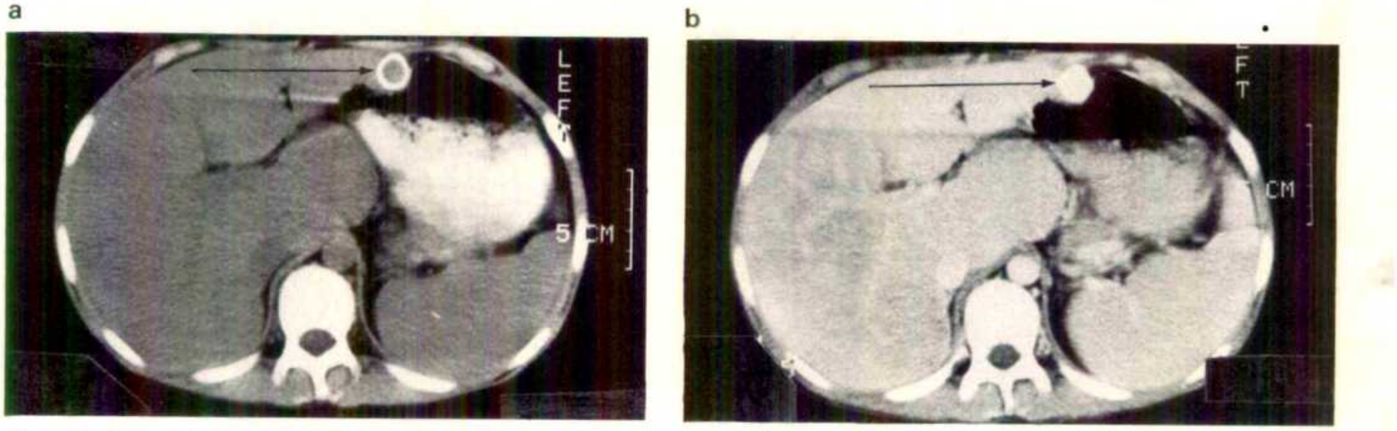

Figure 3 *Computed tomographic scans* **a** *before and* **b** *after contrast enhancement, demonstrating a patent mesoatrial shunt (arrowed)*

Table 2 *Surgical approaches to the Budd–Chiari syndrome*

Portosystemic shunts
Portacaval (side-to-side)[7,22–24]*
Portoatrial[25,26]
Portopulmonary[27]

Splenorenal[6]
Splenoatrial[30]
Splenopulmonary[31]
Splenoazygos[32]
Splenopneumopexy[33]

Mesocaval[14,20,28]*
Mesoatrial[12,13,29]*
Mesopulmonary[8]

Mesocaval + cavoatrial[28]
Cavosplenoatrial[34]
Iliac–mesenteric–atrial[35]
Two-stage mesoatrial/portacaval[8,36]

Direct operations†
Transatrial fracture/excision of caval web[5,37,38]*
Transcaval posterocranial liver resection ± hepatoatrial anastomosis[39,40]
Retrohepatic patch cavoplasty + shunt or hepatic vein balloon angioplasty[41,42]
Retrohepatic caval thrombectomy and patch angioplasty[43]
Percutaneous angioplasty of caval stenosis or web[44–46]
Hepatic/retroperitoneal tumour resection[7]

Orthotopic liver transplantation[47–49]*

Palliative procedures
LeVeen peritoneovenous shunt[7,50]
Sclerotherapy for variceal bleeding

* Most commonly performed procedures; † almost all require extracorporeal circulation

artery blood flow in one patient. Three patients have had repeat cavograms and manometric studies (*Table 1*) demonstrating improvements in caval pressure gradients consequent on caudate lobe decompression.

Discussion

Controversial surgical aspects of the Budd–Chiari syndrome relate firstly to the indications for surgery, secondly to the optimal surgical approach, and thirdly to details of operative technique. The relative rarity of this condition in the West and the consequent absence of controlled clinical trials do not enable any definitive statements on these problems but some conclusions can be drawn from the surgical literature.

It seems likely that surgical treatment is superior to conservative therapy alone[3,6,14] since the majority of patients managed conservatively die within 2–3 years of presentation[9,18], although medical therapy can occasionally be compatible with long-term survival[19]. Few would dispute that medically intractable ascites, rapidly deteriorating liver function and progressive wasting merit surgical intervention. Added to this, Millikan *et al.*[8] have suggested that the presence of severe zone 3 necrosis on a liver biopsy specimen signifies a failing liver and the need for surgical treatment. These indications continue to broaden as the operative mortality of shunt surgery diminishes and postoperative survival increases[20,21]. Furthermore, the improved quality of life with freedom from ascites and the apparent absence of late encephalopathy has prompted several authors to recommend urgent portosystemic shunting in all patients with symptomatic Budd–Chiari syndrome[12,20,21].

The lack of any consensus about the best surgical approach is reflected by the wide variety of operations designed to relieve this condition (*Table 2*). This is related partly to the differing anatomical aetiologies of the Budd–Chiari syndrome; in Japan and China, membranous and segmental obstruction of the IVC are relatively common causes of the syndrome[5,7] and direct operations are more often performed. In contrast, in the West, hepatic vein occlusion is the more usual primary pathology and shunting procedures have tended to be performed. Portosystemic shunting is effective since it converts the portal vein into an outflow tract, thus decompressing the massive hepatic congestion and reducing hepatic sinusoidal pressure towards normal[22]. Side-to-side portacaval shunting is regarded as the method of choice by many[7,8,21,22] but occlusion or obstruction of the IVC, due to thrombosis or caudate lobe compression respectively, either precludes or militates against a successful outcome[3,12,14]. Caudate lobe hypertrophy, which develops because its veins drain directly into the cava independently of the main hepatic veins, frequently makes side-to-side portacaval shunting impossible[23]. Because of these difficulties, mesocaval interposition shunting has been recommended. However, the excellent results reported by Vons *et al.*[20], even with mesocaval pressure gradients as low as 5 mmHg, have not been repeated by others in patients with the Budd–Chiari syndrome[11,14] or in other cases of portal hypertension[51,52]. This may be partly related to the use of autologous vein rather than prosthetic material for the interposition shunt. Even accepting this, however, the patent mesocaval shunt may still fail to control symptoms in the presence of obstruction of the IVC[14,28].

The mesoatrial shunt was first successfully reported by Cameron and Maddrey in 1978[15] although a similar graft connected to an internal iliac artery fistula had been previously described[53]. The objective of the shunt is to provide portosystemic decompression in the presence of an occluded IVC, and the indications have since been extended to include patients with caval obstruction. The haemodynamics of this shunt have recently been reported[54] and our patients demonstrated similar acute changes in cardiac output and portal vein pressure upon opening the shunt. The route for the graft that we adopted involved a median sternotomy rather than a right lateral thoracotomy and we believe this to be a significant advantage since it eliminates the risk of a prolonged pleural leak of ascites[14,25,34]. Some surgeons have criticized this long prosthetic shunt as being prone to thrombosis[8,34,36]. This is partially borne out by reports in the literature (*Table 3*) but these results are likely to improve with the use of externally supported expanded PTFE grafts. This material is easy to handle, is alleged to have a thromboresistant potential, develops

Table 3. *Collected results for mesoatrial shunt surgery*

Reference	No. of patients	Type of graft	Patency	Maximum follow-up
Harris *et al.*[30]	1	10 mm woven Dacron*	Thrombosed (4 days)	—
Wruble *et al.*[29]	1	16 mm woven Dacron	Patent	16 months
Cameron *et al.*[12]	7	16 mm woven Dacron	3/7 thrombosed	60 months
Khanduri *et al.*[13]	3	14–20 mm woven Dacron	Patent	20 months
Warren *et al.*[36]	1	20 mm reinforced PTFE	Patent	4 months†
Chezmar and Bernardino[8,55]	8	Dacron or PTFE	2/8 thrombosed	48 months
Ahn *et al.*[14]	1	Dacron	Thrombosed	4 months
Gentil-Kocher *et al.*[56]	4	PTFE + jugular vein	3 patent (1 postoperative death)	43 months
Total	26		7/25 thrombosed	

* Dacron® is a registered trademark of E.I. du Pont de Nemours and Company. † Converted to portacaval shunt; PTFE, polytetrafluoroethylene

only a thin neointima, and has been used successfully for shunts in portal hypertension and in the Budd–Chiari syndrome[34,57,58]. Moreover, the external spiral reinforcement should eliminate graft compression in the subxiphoid tunnel, which can be a problem[59]. The Impraflex mesoatrial shunt with its high blood flow encouraged by the abdominothoracic pressure gradient, its wide diameter, moderate rigidity and low thrombogenicity fulfils most of the criteria for a successful venous bypass graft[60]. Additionally, the use of maintenance low-dose heparin prophylaxis in these patients may be of further benefit.

However, if doubts about the long-term patency of the mesoatrial shunt are subsequently confirmed, then a two-stage approach to the Budd–Chiari syndrome associated with obstruction of the IVC may be the solution. This would entail an initial mesoatrial shunt which would be replaced by an elective portacaval shunt a few months later when the liver had decompressed and the caval gradient had returned towards normal[8,36]. Another possible alternative, orthotopic liver transplantation, has achieved a 54 per cent 3-year survival rate[48] but hepatic vein rethrombosis is a recognized hazard[9,61].

Shunt patency can be usefully assessed postoperatively by Doppler flow studies of both the shunt and the portal vein (hepatofugal flow), contrast-enhanced CT scanning, magnetic resonance imaging and invasive angiography[55,62,63]. All patients in this series have maintained patent shunts to date. Experimental and clinical data suggest that the hepatic architecture can return towards normal after successful portosystemic shunting[12,22] but there is also a tendency for fibrosis to replace areas of liver cell necrosis[8].

In conclusion, this series of five patients demonstrates the effectiveness of the mesoatrial shunt in patients with the Budd–Chiari syndrome complicated by inferior vena caval obstruction or occlusion. There were no perioperative deaths and all shunts have subsequently remained patent. This success may be partly related to the choice of externally reinforced expanded PTFE for the prosthetic graft. The long-term patency of such shunts is likely to be a major factor in influencing the choice of therapy in the Budd–Chiari syndrome.

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General practice-based population screening for abdominal aortic aneurysms: a pilot study

T. J. O'Kelly and B. P. Heather

Department of Surgery, Gloucester Royal Hospital, Great Western Road, Gloucester GL1 3NN, UK

Correspondence to:
Mr B P. Heather

All 1195 male patients aged between 65 and 74 years on the Family Practitioner Committee register for the four group practices in Stroud, UK were invited for a health screening check. The examinations included abdominal ultrasonography to measure maximum aortic diameter, measurement of blood pressure and recording of smoking habits. An attendance rate of 76 per cent was achieved (906 patients). Seventy-one patients (7·8 per cent) were found to have aortic diameters >2·5 cm and 14 (1·5 per cent) had aortic diameters >4·0 cm. Aneurysms were more common in smokers and in hypertensive patients. However, restriction of screening to patients with these risk factors would have led to a number of aneurysms remaining undiscovered. We recommend therefore that ultrasound screening for abdominal aortic aneurysms should be offered to all men between the ages of 65 and 74 years.

Keywords: Abdominal aortic aneurysm, ultrasound screening, population surveillance

Population screening for abdominal aortic aneurysms, with elective repair of the aneurysms so discovered, would prevent their rupture and reduce the number of deaths from this cause. Men between the ages of 65 and 74 years are recognized as a suitable target population, and an ultrasound-based programme for screening these individuals has been proposed[1]. To study this further, a pilot project of population surveillance in Stroud, UK was undertaken to look at the practicalities of screening, the distribution of aortic diameters and the relevance of risk factors such as smoking and hypertension.

Patients and methods

All men born in the years 1913–22 inclusive, residing in the Stroud area and appearing on the Family Practitioner Committee records of Stroud's four general practices, were invited for screening

Invitations in their names were printed on the general practitioner's notepaper and sent out informing the named recipient of conditions common in their age group, such as hypertension and vascular disease. It was suggested that these conditions could be detected by rapid, simple and painless means and that effective treatment could be offered. Each individual was given a specific appointment and all patients were screened at their own general practitioner's premises during afternoon or evening surgery hours. No attempt was made to follow up non-attenders

Screening was performed by a senior radiographer with special ultrasound training and a state registered nurse. Patients were seen at 5-min intervals and had their height, weight and blood pressure measured before abdominal ultrasound. Smoking habits were recorded

Ultrasonography was performed using a portable B mode grey scale machine and 3·5 MHz linear array probe (Philips SDR1200, Philips Ultrasound Incorporated, Santa Ana, California, USA) Hard copies were made of significant scans using a thermal imager Aortic measurement was taken from the outer margin of the anterior aortic wall echo (A) to the inner margin of the posterior aortic wall echo (P) and the maximum A–P diameter was recorded.

All examinations were completed within a 12-week period by holding three afternoon or evening sessions per week.

It was agreed before the study that all patients with an aortic diameter >4·0 cm would automatically receive an out-patient appointment with a consultant vascular surgeon (B P H) for consideration of elective surgery.

On the assumption that they represent a group with a high risk of future frank aneurysmal dilatation, subjects with aortic diameters between 2·6 and 4·0 cm have been entered into an ongoing study and will be seen again at 6-monthly intervals for repeated ultrasound examination Patients in this group were each given a careful verbal and written explanation of the findings and of our intention to send them a further appointment for repeat ultrasound examination

The χ^2 test was used with Yates' correction to compare patients for different risk factors.

Results

Records for the four participating group practices contained the names and addresses of 1195 men born in the years 1913–22 inclusive Of these, 906 attended for examination, an attendance rate of 76 per cent. Inaccuracies were found in the records which included a number of patients who had died or changed address. The true attendance rate of patients successfully contacted was in excess of 80 per cent.

Confident aortic diameter measurement was made in each of the 906 patients attending, and the findings are summarized in *Table 1*. Anteroposterior aortic diameters >2·5 cm were found in 71 patients (7·8 per cent) and 14 patients (1·5 per cent) had A–P diameters >4·0 cm. Aortic diameters >2·5 cm and >4·0 cm were discovered throughout the age range examined. There was no statistically significant difference in the incidence of large aortas between the younger and the older halves of the population examined. There appears to be a slight tendency for mean aortic diameter to increase with age, although this achieves statistical significance only when patients born in 1913 are compared with those born in 1922 ($P < 0{\cdot}02$, unpaired Student's t test).

Risk factors which might be used to select patients for aneurysm screening are examined in *Table 2*. Aortic diameters >4·0 cm were significantly more common in smokers ($\chi^2 = 5{\cdot}5$, $P < 0{\cdot}02$) and in patients with systolic blood pressure >180 mmHg ($\chi^2 = 4{\cdot}4$, $P < 0{\cdot}05$), although cut-off points of 90, 100 and 110 mmHg for diastolic pressure failed to demonstrate any significant difference in aneurysm incidence Of much greater practical importance is the fact that 6 of 14 aortas >4·0 cm were discovered in current non-smokers, 8 of 14 were in patients with systolic blood pressures <180 mmHg, and 7 of 14 were in patients with diastolic blood pressures <90 mmHg. Four patients with aneurysms were in low risk categories for all three criteria.

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Table 1 *Distribution of aortic diameter in 906 men aged 65 to 74 years*

Birth year	*n*	Aortic diameter (cm) Mean	s.d.	Median	Range	No. of large aortas >2·5 cm	>4·0 cm
1913	75	2·1	0·7	1·9	1·4–5·9	9	2
1914	66	2·0	0·5	1·9	1·4–4·2	5	1
1915	71	2·1	0·6	1·9	1·5–5·1	4	3
1916	83	2·1	0·5	2·0	1·4–4·7	13	1
1917	73	2·0	0·6	1·9	1·3–4·7	6	2
1918	71	2·0	0·5	1·9	1·2–5·3	6	1
1919	88	2·0	0·4	1·9	1·5–3·7	7	0
1920	143	2·0	0·5	1·9	1·4–5·3	8	2
1921	118	2·0	0·4	2·0	1·4–4·3	11	1
1922	118	1·9	0·4	1·8	1·3–5·5	2	1
Total	906	2·0	0·5	1·9	1·2–5·9	71	14

Table 2 *Risk factors for aneurysms*

	Aortic diameter <2·6	2·6–4·0	>4·0
Smokers (*n* = 237)	207	22	8
Non-smokers (*n* = 669)	628	35	6
Systolic BP >180 mmHg (*n* = 163)	145	12	6
Systolic BP ⩽180 mmHg (*n* = 743)	690	45	8
Diastolic BP >90 mmHg (*n* = 293)	270	16	7
Diastolic BP ⩽90 mmHg (*n* = 613)	565	41	7

BP, blood pressure

Discussion

This pilot study has demonstrated that large-scale population screening for abdominal aortic aneurysms is feasible and productive.

An attendance rate of approximately 80 per cent after a single invitation letter compares favourably with the best results from breast cancer screening[2] and is double that achieved in a previous population screening project for abdominal aortic aneurysms in which invitations and examinations were hospital based[3]. We have no doubt that the participation of general practitioners in both sending out invitation letters on their notepaper and holding screening sessions at their practice premises rather than in hospital has contributed significantly to the high attendance. The importance of the role of general practitioners in increasing attendance for screening has been shown previously[4]

The 1·5 per cent incidence of aneurysms suitable for consideration of elective repair shown in this study is somewhat lower than that found in other series. Nevertheless, we feel that the detection rate is both high enough to justify the implementation of a permanent district screening programme and low enough that the additional surgical workload could reasonably be accommodated within existing facilities.

All the examinations were carried out rapidly, efficiently and confidently by a nurse and a radiographer. Although one of the authors was present at each of the sessions, we have no doubt that future sessions could be organized without a doctor in attendance, thus keeping the cost of screening to a minimum

This study neither considers the fate of patients with aortic diameters between 2·6 and 4·0 cm nor does it establish if a normal aortic diameter measurement at the age of 65 or 66 years offers complete freedom from future risk of aneurysmal dilatation. These are important considerations in the design of a long-term screening programme.

A suitable population for aneurysm screening might be selected on the basis of known or presumed risk factors such as age, sex, smoking habits, hypertension or family history. Our study has been selective in screening only men, because of their significantly higher aneurysm risk, and in choosing an age group old enough to have an appreciable aneurysm incidence yet young enough to undergo elective repair. We have recorded only current smoking habits as admitted by the patient without biochemical confirmation and have taken a single blood pressure reading without details of antihypertensive medication. Within these, admittedly limited, definitions of smoking and hypertension, we have found aneurysms in non-smokers and in patients without high blood pressure. These aneurysms would have remained undetected had the selection criteria of smoking and hypertension been applied.

An aneurysm screening service can be run at reasonable cost by a nurse and a radiographer using inexpensive portable equipment and working without direct medical supervision. High attendance rates could be anticipated at screening sessions held at the invitation of general practitioners at their own health centre. Significant numbers of asymptomatic aneurysms would be detected and elective repair should reduce mortality from aneurysm rupture. Selection of patients for screening on the basis of smoking or hypertension is unnecessary and risks a proportion of aneurysms remaining undetected.

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Clinical and histological sequelae of Roux-en-Y diversion

M. J. Hollands, I. Filipe, S. Edwards, K. Brame, M. Maisey and W. J. Owen

Departments of Surgery, Pathology, Medical Physics and Nuclear Medicine, United Medical Schools of Guy's and St. Thomas' Hospitals, St. Thomas' Street, London SE1 9RT, UK

Correspondence to:
Mr M. Hollands, Department of Surgery, Westmead Hospital, NSW 2145, Australia

Nine post-Polya gastrectomy patients with symptoms of reflux gastritis were studied immediately before and 6 months after Roux-en-Y diversion with a 60 cm jejunal loop. Endoscopy, histology, HIDA radionuclide studies and acid secretory studies were performed to determine the effect of Roux-en-Y diversion. Symptomatic results were pleasing in that all patients were graded as Visick I or II. There was a statistically significant improvement in endoscopic evidence of mucosal damage (median score of 6 reduced to median of 1) and visible bile reflux (median score of 10·5 reduced to 0). Foveolar hyperplasia, superficial chronic gastritis and histological precursors of malignancy all improved. There was a significant decrease in the reflux of ^{99m}Tc-labelled HIDA into the gastric remnant while acid secretion remained unchanged. Roux-en-Y diversion with a 60 cm jejunal loop provides not only symptomatic relief but scintigraphic, endoscopic and histological evidence of pancreatobiliary diversion.

Keywords: Roux-en-Y diversion, reflux gastritis, symptoms, gastric histology, endoscopy, scintigraphy

Surgical diversion of the duodenal contents with a 60 cm Roux-en-Y loop is now the treatment of choice for patients with postgastrectomy reflux gastritis. Unfortunately the results of surgical diversion are often disappointing[1,2]. Unsatisfactory results may be due to poor patient selection, incomplete diversion of the duodenal contents or the complications of the procedure chosen to achieve surgical diversion.

Adequate surgical diversion should result in symptomatic improvement and also an improvement in the objective indices of reflux, namely endoscopic and histological appearances, and a reduction of enterogastric reflux as determined by HIDA (^{99m}Tc-Sn-2,6-diethylacetanilidoiminodiacetate) scanning. This paper addresses the problems of what constitutes adequate diversion.

Patients and methods

Patients

Nine patients (six men and three women) aged from 62 to 84 years (median 72 years) were studied prospectively immediately before and 6 months after a 60 cm Roux-en-Y diversion was performed for postgastrectomy reflux gastritis. All the patients complained of epigastric pain and bile vomiting after Polya gastrectomy 6–32 years previously. In all patients these symptoms could be provoked by instillation of the duodenal contents into the gastric remnant[3]. Three patients had a previous cholecystectomy before their gastrectomy and three had a truncal vagotomy either at the time of gastrectomy (one patient) or as a subsequent therapeutic manoeuvre aimed at resolving symptoms of reflux (two patients). Upper gastrointestinal endoscopy, gastric and oesophageal biopsy, pentagastrin acid stimulation tests and HIDA scans were performed before and 6 months after Roux-en-Y diversion.

Operation

A 60 cm Roux-en-Y jejunal loop was used to divert the duodenal contents. The afferent loop was divided at the stomach and reanastomosed end-to-side 60 cm distally along the efferent loop. In one patient a Tanner 19 modification was used. A truncal vagotomy was performed routinely.

Endoscopy

All the patients were endoscoped by two of the authors (M.J.H. and K.B.). K.B. was unaware of the diagnosis. We used an Olympus end viewing GIF Q gastroscope* with lecturescope teaching attachment which allowed independent but simultaneous assessment. Mucosal damage and evidence of visible reflux were assessed by each endoscopist. Indices of mucosal damage were erythema, hyperaemia, friability, granularity and contact bleeding. The extent of visible reflux was determined by the presence of waves of reflux across the stoma, bile pools between the rugae and bile staining of mucus.

Each endoscopist scored evidence of mucosal damage and visible reflux on a scale of 0–6 around the stoma and in the body of the stomach. These two scores were summed to give a mucosal damage and reflux score for each endoscopist. The two endoscopists' scores were then averaged to give a mucosal damage score and visible reflux score for the gastric remnant.

Histology

Biopsies were collected after each endoscopy. At least two random specimens were taken from the stoma and two from the gastric body. Additional biopsies were taken from any obviously abnormal area. Specimens were immediately fixed in 10 per cent formal saline, processed routinely and later stained with haematoxylin and eosin. Additional stains with Alcian blue/PAS and high iron-diamine/Alcian blue (HID–AB) were used to detect and classify intestinal metaplasia[4]. Histological changes were scored by I.M.F. and M.J.H. (I.M.F. was unaware of the diagnosis or the operative status of the patient) using a modification of a system used in previous studies[5].

Three categories of histological change were identified.

1. Foveolar hyperplasia is said to be the result of bile reflux and is characterized by elongation and tortuosity of the gastric pits[6]. We scored it as absent (0), mild (+), moderate (+ +) or severe (+ + +).

2. Superficial chronic gastritis may reflect injury and regeneration. It may be associated with an inflammatory infiltrate, pseudopyloric metaplasia, cystic degeneration and oedema, vasodilatation and infiltration of muscle fibres into the lamina propria. Like foveolar hyperplasia we scored it on a scale from 0 to + + +.

The foveolar hyperplasia and superficial chronic gastritis scores were combined (maximum = 6), giving a reflux gastritis score.

3. Possible precursors of malignancy; we recognized three features of mucosal morphology as suggestive of an increased risk of malignancy: chronic atrophic gastritis, intestinal metaplasia and dysplasia[7]. The definition and grading of dysplasia was based on the criteria outlined by Morson *et al.*[7].

Chronic atrophic gastritis was scored on a scale from 0 to + + +. Intestinal metaplasia was classified into three types on the basis of cell differentiation and the presence or absence of sulphomucin secretion[8]. If present it was scored as for chronic atrophic gastritis. The presence (score = 1) or absence of dysplasia was noted. A score indicating the extent of premalignant change (maximum = 7) was calculated.

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* *Olympus Optical Company, Keymed, Southend, UK*

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Oesophageal biopsies were also collected from a point 5 cm above the gastro-oesophageal junction. Five features of altered oesophageal histology were noted: inflammatory cell infiltrates in the lamina propria, cellular atypia, haemorrhage, basal cell hyperplasia and elongation of the papillae. The first three features were noted to be present (score = 1) or absent. The basal zone should be less than 15 per cent of the total thickness of the epithelium[9]. If it exceeded 20 per cent the specimen was considered abnormal (score = 1). Papillary height was felt to be normal if the papillae extended over less than 50 per cent of the epithelial thickness but abnormal if between 50 and 75 per cent of the thickness (score = 1). If the papillae extended over more than 75 per cent of the epithelial span a score of 2 was recorded. This left a total possible score of 6.

Radionuclide scans

A dose of 200 MBq ^{99m}Tc-labelled diethyl HIDA was injected intravenously. An ^{111}In-labelled diethylenetriamine pentacetic acid (DPTA) fatty meal was administered 30 min later. If a cholecystectomy had previously been performed this time interval was reduced to 20 min. The fatty meal consisted of one sachet of Build Up®, 23 g Casilan® (Farley Health Products Ltd., Plymouth, UK), sugar to taste, 25 ml Prosparol® (Duncan, Flockhart and Company Ltd., Greenford, UK), 20 MBq ^{111}In-labelled DTPA and 300 ml water.

The fatty meal served to identify the gastric area of interest, instigate gallbladder contraction and provide a measure of gastric emptying. The patient was imaged using a large field of view γ camera set up to separate the photopeaks of ^{99m}Tc and ^{111}In using a narrow 12 per cent window. Immediately after finishing the meal the patient was positioned under the camera in a semi-recumbent position and the data were collected for 1 h at 1 frame/min using small area dual isotope acquisition.

Results were analysed by first drawing areas of interest over the stomach and over part of the right lobe of the liver. Activity–time curves were plotted for these regions separately for the two isotopes. The curves corresponding to the ^{99m}Tc photopeak window were corrected for crossover from the higher energy ^{111}In by subtracting a previously established constant fraction (0·51) of the ^{111}In curves.

The corrected ^{99m}Tc stomach curve was then further corrected to remove the effect of the left lobe of the liver. This was achieved by subtracting a multiple of the ^{99m}Tc liver curve from the ^{99m}Tc stomach curve such that the resultant curve was zero in the first frame. This manoeuvre was justified as long as there was no reflux in the first frame.

The area under the resultant, doubly corrected curve gave an indication of the quantity and duration of reflux of ^{99m}Tc-labelled bile into the gastric remnant over the duration of the test. This area was calculated using Simpson's formula as total counts per frame over 60 min using a dBase II® computer program (Ashton-Tate, Maidenhead, UK).

Acid secretory studies

Only eight patients agreed to a second pentagastrin test. After an overnight fast a 16 Fr nasogastric tube was passed with fluroscopic control into the gastric remnant. Basal acid output was collected in 4 × 15 min samples. A dose of 6 µg/kg of subcutaneous pentagastrin was given and a further 4 × 15-min samples collected. Three patients had a previous vagotomy and were given 12 µg/kg of pentagastrin. After Roux-en-Y diversion and truncal vagotomy all patients were given 12 µg/kg of pentagastrin. Samples were collected by continuous hand suction.

Anacidity was defined as a pH not less than 7 after stimulation with pentagastrin[10]. Basal acid output was calculated from the four basal collections. Peak acid output is said to represent the closest approximation to the maximum capacity to secrete acid[11]. It was calculated from the sum of the two highest consecutive samples[12]. All acid outputs were expressed as mmol/h.

Statistics

This population of patients probably does not conform to a 'normal' distribution and the median has been used as a measure of central tendency. The test of significance chosen was the signed rank non-parametric test as each patient acted as their own control.

Calculations were made using a Stats Plus® program (Human Dynamic Systems, California, USA) on an Apple IIe® computer (Model AZM 2010P, Apple Computer Company, Cupertino, California, USA).

Results

Operative results

All nine patients were pleased with the results of their operation and were graded as Visick Grade I or II. No patient had persistent pain or bile vomiting. Four patients had no complaints and a fifth was perfectly well until an adenocarcinoma of the prostate was diagnosed 18 months after his operation. Two of the other four patients had mild diarrhoea and two others occasionally experienced epigastric fullness and nausea. One patient was disappointed because he thought he had failed to gain weight although he had actually gained 2·8 kg. No patient had symptoms of sufficient severity to interfere with their lifestyle.

Endoscopy

The score for mucosal damage decreased from a median of 6 (range 1·5–10·5) to a median of 1 (range 0–3·5). Visible reflux also decreased from a median of 10·5 (range 1–12) to a median of 0 (range 0–4). Both these decreases were statistically significant ($z=-2{\cdot}43$, $P=0{\cdot}015$; $z=-2{\cdot}55$, $P=0{\cdot}011$, respectively).

The sum gastric endoscopic score also decreased from a median of 16 (range 2·5–22·5) to a median of 1 (range 0–7·5). This difference is statistically significant ($z=-2{\cdot}55$, $P=0{\cdot}011$).

Histology

Before Roux-en-Y diversion foveolar hyperplasia was present in the biopsies of all but one patient. The scores ranged from 0–3 with a median score of 1. After diversion foveolar hyperplasia was no longer seen in any of the biopsies. Superficial chronic gastritis improved in all patients. The median score decreased from 3 (range 0–3) to 1 (range 0–1). Overall the reflux gastritis score decreased from a median of 4 (range 3–6) to a median of 1 (range 0–1). This difference is statistically significant ($z=-2{\cdot}67$, $P=0{\cdot}007$).

Chronic atrophic gastritis also improved. Before Roux-en-Y diversion the scores ranged from 0–3 with a median of 1. After diversion chronic atrophic gastritis was less pronounced: the scores ranged from 0–1 with a median score of 1. Four of the nine patients had evidence of intestinal metaplasia before Roux-en-Y diversion. No patient had Type III intestinal metaplasia. Mild dysplasia was present in one patient. Intestinal metaplasia and dysplasia were not seen after Roux-en-Y diversion.

If the individual preoperative scores for the three possible precursors of malignant change were added together (maximum = 7), the scores ranged from 0 to 5 with a median of 2. After diversion the median score was 0 with a range of 0–1. This was a statistically significant improvement ($z=-2{\cdot}52$, $P=0{\cdot}011$).

The net oesophageal score ranged from 0–4 (median 3) before Roux-en-Y diversion but, postoperatively, improvement was noted in all except one patient. The range of scores remained 0–4 but the median score fell to zero. The difference reaches statistical significance ($z=-2{\cdot}38$, $P=0{\cdot}016$).

Prior cholecystectomy and vagotomy did not appear to influence the histological changes.

HIDA scans

Reflux of ^{99m}Tc-labelled HIDA into the gastric remnant decreased from a median of 2566 counts (range 631–15509) to a median of 58 counts (range 0–2926). This decrease (median 96 per cent) is statistically significant ($z=-2{\cdot}38$, $P=0{\cdot}017$).

Acid secretory studies

Three patients remained anacid after Roux-en-Y diversion and truncal vagotomy. There was no significant increase in basal acid output (median 0 mmol/h, range 0–0·73, $P=0{\cdot}59$) or peak acid output (median 0·55 mmol/h, range 0–4·94, $P=0{\cdot}68$) 6 months after diversion.

Discussion

The treatment of postoperative reflux gastritis remains a problem. The chances of a successful operative outcome range from 100 per cent to less than 60 per cent[2,13]. Evidence from animal experiments has demonstrated an association between gastritis and exposure to different enteric juices[14–18]. Subsequent surgical diversion of these juices improves the gastritis[19]. Such animal evidence offers strong theoretical support for the use of surgical diversion of duodenal contents in the treatment of postoperative reflux gastritis in man.

The results of subsequent patient studies are contradictory. Although the presence of duodenal contents in the gastric remnant may evoke a symptom response[3,20], there is no clear association between endoscopic and histological findings and symptoms after gastrectomy. Subsequent surgical diversion may improve both symptoms and the endoscopic appearance[13,21–24]. Our study has confirmed these findings.

Hoare *et al.*[22] have suggested that reflux causes the gastric mucosal erythema seen endoscopically in patients with reflux gastritis. Our study supports this finding. Endoscopic evidence of mucosal damage including erythema and visible reflux improved significantly after Roux-en-Y diversion.

The histological response to Roux-en-Y diversion remains controversial. This study, and others, have demonstrated that foveolar hyperplasia will regress in man and animals after diversion of the duodenal contents[19,24]. As in a previous study[25] this effect was independent of vagotomy in our patients.

Gastritis, which is an almost universal finding after gastrectomy[26–29], was seen to improve after Roux-en-Y diversion in our study and one other[30]. This is contrary to most previous work[22,24,31]. The length of follow-up in our study is no different from other studies where follow-up ranged from 3 to over 12 months. We did not take fewer biopsies than other studies and our data are thus no more prone to sampling errors Day-to-day and individual variations in reporting mucosal changes were also considered and the histology of eight random patients was re-reported firstly by I.M.F. and then by another histopathologist without significantly altering our findings

There are two other possible reasons which might explain the difference between our results and those of other published series. One may be the adequacy of surgical diversion and the other might be the specific features of gastric mucosa as studied by different authors.

There is an increasing body of evidence demonstrating a strong correlation between high concentrations of intragastric bile acids and mucosal abnormalities including gastritis[30,32,33]. Most previous work has concentrated on the inflammatory aspects of gastritis. Recently Dixon *et al.* have described 'reflux' gastritis as being characterized by foveolar hyperplasia, a paucity of inflammatory cells, oedema, increased numbers of smooth muscle fibres, and vasodilatation in the lamina propria[34]. Our work has been in progress since 1982 as long term follow-up was required. However, our system of scoring is not unlike that of Dixon *et al* [34]. In all patients in whom reflux was abolished the features of reflux gastritis resolved. This finding would support the conclusion of Dixon and colleagues that reflux gastritis is a distinct pathological entity[34]. Furthermore it explains why such variable results have been reported on the effects of Roux-en-Y diversion on the gastric mucosal morphology.

If histological evidence of reflux gastritis is to decrease, surgical diversion of the pancreatobiliary secretions must be adequate. In those studies where there was no histological improvement the length of Roux-en-Y loop chosen to achieve surgical diversion was usually less than 50 cm[22,24,31]. In our patients, using a 60 cm loop, there was also convincing endoscopic and scintigraphic evidence that adequate surgical diversion had been achieved.

Chronic atrophic gastritis, intestinal metaplasia and dysplasia may be significant features of premalignant change[7]. Gastric mucosal atrophy may be found in a healthy population[35] but enterogastric reflux is probably the most important factor in its pathogenesis[36]. If so, diversion of the enteric contents should lead to an improvement of gastric mucosal morphology. Some support for this hypothesis may be found in a case report from Bristol[37] where a patient with almost complete achlorhydria secondary to enterogastric reflux was treated with antrectomy and Roux-en-Y diversion. Normal acid secretion had returned 4 months later. Conversely a study from Belfast[31] failed to show any improvement in atrophic gastritis after Roux-en-Y diversion. The authors did not state the length of their loop, though a previous study from the same unit[38] used an 18–40 cm Roux-en-Y loop In our patients, using a 60 cm loop with a scintigraphically proved reduction in HIDA-labelled reflux, chronic atrophic gastritis appeared to be less extensive after Roux-en-Y diversion.

Another possible explanation may be the definition of what constitutes gastric atrophy. Watt *et al.*[31] scored atrophy as a loss of specialized cells. We included other features of the mucosal morphology including cystic degeneration, chronic inflammatory infiltrate and intestinal metaplasia.

A further factor may be the presence or absence of a gastric antrum. Independently, Lawson[39] and Witt *et al.*[18] have shown that antrectomy leads to epithelial hypoplasia in dogs. In turn, reflux of the duodenal contents damages this epithelium and the subsequent gastritis is more severe than in animals with an intact antrum. Watt *et al.*[40] detected some differences in the effect of Roux-en-Y diversion (no antrum) compared with closure of a gastrojejunostomy (antrum intact). All our patients had a prior antrectomy. Five of the nine patients had varying degrees of gastric atrophy. There was no correlation between the degree of atrophy and the time span after gastric surgery. After diversion of the duodenal contents the gastritis and the atrophic appearance of the mucosa improves. This result implies that gastric atrophy may be reversible, even in the presence of antrectomy, if the damaging agent is withdrawn.

Intestinal metaplasia may be an advanced stage of chronic atrophic gastritis[41] but only one type, Type III, may be premalignant[42]. In our study no patient had Type III intestinal metaplasia. Although four patients had evidence of intestinal metaplasia in their pre-Roux-en-Y biopsy, none showed intestinal metaplasia after diversion. This is a new finding but is compatible with Tympner *et al.*'s[43] conclusion that intestinal metaplasia is associated with increased reflux. It may also be explained by the small size of our series or a sampling error. With this in mind we reviewed the gastric histology of five other post-Roux-en-Y diversion patients who we had not studied prospectively. None of these patients had intestinal metaplasia.

Dysplasia is also frequent after gastrectomy[27,29,31,44,45]. Its severity may be correlated with scintigraphic evidence of duodenogastric reflux[45]. The apparent frequency of dysplasia, however, may be misleading as it is easily confused with foveolar hyperplasia[34]. Only one of our patients, had evidence of dysplasia and this precludes a useful contribution to this debate.

Whether duodenogastric reflux causes postgastrectomy gastric cancer or not remains controversial. Adequate Roux-en-Y diversion, in our patients, appeared to reduce the extent and severity of many of those histological changes considered by some to be precursors of malignant change. Time after diversion does not appear to influence the mucosal changes noted As mentioned previously, we studied five other patients up to 3 years after Roux-en-Y diversion and all appeared to have relatively normal gastric mucosa. More patients need to be studied using a Roux-en-Y loop of sufficient length to ensure adequate diversion of the duodenal contents if this question is to be resolved.

Oesophageal histology in our patients improved after diversion of the duodenal contents as it did in the study by Hoare *et al.*[22]. Ismail-Beigi *et al.*[9] have suggested that the histological features of oesophagitis – papillary elongation and basal cell hyperplasia – are features of increased cell loss and replacement following desquamation of the superficial layers of the epithelium by reflux of the gastric contents. Their patients were refluxing acid, but bile and trypsin have also been shown to have a toxic effect on the oesophageal mucosa[46,47,48] and represent the probable mechanism of injury in our patients Adequate diversion of bile led to a marked improvement in these histological features of mucosal damage.

A 60 cm Roux-en-Y afferent loop diversion successfully reduced ^{99m}Tc-labelled HIDA bile reflux into the gastric remnant Excellent symptomatic relief was accompanied by endoscopic and histological evidence of a return towards normal in the gastric remnant.

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Intra-abdominal lymphangioma

I. Roisman*, J. Manny*, S. Fields† and E. Shiloni*

*Departments of Surgery A and *B and †Department of Radiology, Hadassah University Hospital, Jerusalem, Israel*

Correspondence to:
Dr I. Roisman, Department of Surgery A, Hadassah University Hospital, PO Box 12000, il-91120
Jerusalem, Israel

The historical background, aetiology, clinical features, radiographic findings and treatment of abdominal lymphangiomas are reviewed. The condition may give rise to the acute surgical abdomen.

Keywords: Retroperitoneal lymphangioma, acute surgical abdomen

Intra-abdominal cystic and cavernous lymphangiomas are rare benign tumours, usually found incidentally through lymphangiography, during elective abdominal surgery, in an acute surgical abdomen, or at post-mortem examination. The incidence of such tumours has been estimated to range from 1 per 27 400 to 1 per 100 000 hospital admissions[1–3].

Historical background

Braquehaye[4] credited Benievine, a Florentine anatomist, as being the first to note a mesenteric cyst during a post-mortem examination in 1507. Slocum[5] has stated that the earliest description of a chylous cyst, found at necropsy, was published by Rokitansky in 1842. Millard and Tillaux[6] in 1880 were the first to report on the successful treatment of a patient with a mesenteric cyst. According to Walker and Putnam[1], omental cysts were not described until Gairdner's report in 1852. This type, which is believed to be less common than mesenteric cysts, has been estimated to occur from three to ten times more frequently[1]. Pean in 1883, as quoted by Slocum[5], was the first surgeon to record the recovery of a patient who had a lymphangiomatous cyst treated by marsupialization. The initial American report of a chylous cyst of the mesentery was presented by Carson in 1890[7]. Some years later, Sarwey[8] successfully excised a unilocular chylous cystic lymphangioma located in the region of the head of the pancreas of a 9-year-old girl Gaudier and Gorse[9] in 1913 surveyed the accumulated relevant literature, and included a 4-year-old patient of their own with a mass in the right lumbar region which was excised successfully. They claimed this to be the first description of a case of retroperitoneal cystic lymphangioma to appear in print. In 1941 Loeb[19] reviewed the literature on mesenteric cysts and estimated that reports on 550–600 patients had been published. Bearhs *et al.*[11], reporting from the Mayo Clinic, found only nine cases undergoing surgery between the years 1911 and 1947. Pack and Tabah[12], discussing over 870 patients with primary tumours of the retroperitoneum, including 120 of their own, found only five with cystic tumours. Harrow[13] estimated that of more than 600 patients with mesenteric cysts, 70 of whom had retroperitoneal cysts, only 14 fitted the criteria for lymphatic cystic tumours. Rauch[14] screened the literature and added two male patients aged 17 and 10 years with retroperitoneal lymphangiomas. Henzel *et al.*[15] gave an excellent overview of the published material on intra-abdominal lymphangiomas, while adding a 20-year-old patient treated by them.

Aetiology

Sabin[16] divided the development of the lymphatic system into two stages:

1. The primary stage which encompasses the development of isolated lymph sacs derived from veins that are united by the thoracic duct
2. The second stage, which involves peripheral growth of lymph vessels that sprout from the endothelial lining of the sacs. The lymph sacs are transformed into a plexus of lymphatic capillaries by bridging of the lumen with bands of connective tissue from which chains of lymph nodes are derived.

Numerous theories have been proposed concerning the origin of cystic lymphangiomas. Barnett and Branch[17] summarized these theories on the following aetiological basis:

1. Retention, which explains the lymphangioma on the basis of mechanical pressure
2. Disturbance of the endothelial secretory function of the vessels or of endothelial permeability
3. Inflammatory background
4. Embryonal origin.

The last theory, favoured by Barnett and Branch[17], explains the lymphangioma on the basis of a defect in embryonal organization of the lymphatic system. Some investigators express the opinion that retroperitoneal lymphangiomas arise from obstruction of existing lymphatic channels by an inflammatory fibrotic process or lymphatic hamartoma[18]. In general, the majority of authors subscribe to the last two theories.

Godart[19] believes that the aetiology is related to an abnormal development of the lymphatics in that there is failure of communication of a branch, or branches, with the central system, thus explaining why cystic lymphangiomas are found in the same position as fetal lymph sacs (cervical, mediastinal and retroperitoneal). He proposed that lymphatic spaces in the embryo fail to join the venous system, thus producing cysts. Elliot *et al.*[20] believe that lymphaticovenous shunts exist in the perinodal tissues as congenital deficiencies, their formation resulting in cysts.

Other suggested aetiologies include failure of the leaves on the mesentery to fuse or localized degeneration of lymph nodes[2]. Trauma has also been offered as a possible cause of lymphangioma[21,22].

Ewing[23] stated that retroperitoneal lymphangioma occurs in both children and adults as cystic tumours, originating along the spinal column and ramifying into the pelvis behind the kidney or colon, upward to the liver and spleen, as well as into the omentum. He included in this entity a variety of slowly growing congenital tumours of the skin and subcutaneous tissue, neck muscles, axilla, trunk, lip, tongue, eye and orbit.

Lymphangiomas that arise in the retroperitoneal space

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separate the leaves of the mesentery as they grow anteriorly and take up a mesenteric position, or they may push posteriorly in their development, to be recognized only as retroperitoneal tumours. They may encroach on the adjacent structures, including gastrointestinal organs, and so lead to partial obstruction.

Occasionally it is impossible to distinguish between retroperitoneal lymphangiomas and mesenteric cysts, as both these tumours may extend from the retroperitoneum into the mesentery[24] and, moreover, also have the same gross appearance. With these difficulties in mind, Takiff *et al.*[25] stressed the importance of differentiation between these two lesions in view of the fact that lymphangiomas often behave in an aggressive manner and invade the adjacent structures. They observed that lymphangiomas are principally a disorder of childhood and young adulthood, while mesenteric cysts may occur at all ages, although they are mainly found in the fourth decade of life.

Histologically, these two lesions differ. Cystic lymphangiomas display a single endothelial lining, foam cells, innumerable lymphatic channels between lobules of adipose tissue, fibrous and lymphoid tissue, blood vessels and smooth muscle[13,26]. The lining cells of the mesenteric cysts, on the other hand, are often cuboidal or columnar or, on rare occasions, may even be entirely absent.

While lymphangiomas are histologically benign, two patients with lymphangioendotheliomas have been reported[11]. Malignant lymphangiomas are known as lymphangiosarcomas[27]. A unique case of a retroperitoneal malignant tumour in a 44-year-old man has been described recently[28]. The tumour had infiltrated the duodenum and the head of the pancreas, and pancreatoduodenectomy was performed[28].

Classification

Lymphangiomas are classified primarily on a histological basis. The original classification established by Wegner in 1877[29], which is still considered to be the most reliable one[13,14,17,30–34], divides lymphangiomas into simple, cavernous or cystic tumours.

The simple form represents a new growth of small lymphatic channels lined with endothelium, usually situated superficially in the skin. This type consists of an ill-defined mass composed of dilated lymph vessels with rich cellular connective tissue stroma. It has a moderate number of channels through which it is connected to the adjacent lymphatic system.

The cavernous type comprises communicating lymph-filled locules separated by septa and found chiefly in macroglossia, macrocheilia and, more rarely, in other parts of the face and skin. This kind of lymphangioma is a spongy, compressible tumour with dilated lymph vessels and lymphoid stroma, having a moderate number of channels which connect it to the normal lymphatic system.

The cystic type may be uni- or multilocular and appears mainly in the neck, breast, axilla, lower sacral region, abdomen, thighs and inguinal region. When located in the mesentery, cystic lymphangiomas often contain chyle and are appropriately termed chylangiomas or 'chylous cysts'. The tumour is composed of one or many variously-sized cysts ranging from 1 mm to 5 cm in diameter, often communicating with each other[35], and lined with endothelium. The cyst may contain clear chylous, serous, bloody, purulent or chocolate-coloured fluid. Such cystic tumours have practically no connection with normal adjacent lymphatics. They may arise from cavernous forms in which one compartment enlarges, breaking the septa and compressing the other compartment[13]. Gerster[36] maintains that it is not always possible to draw a sharp line between cystic and cavernous lymphangiomas, since the former may contain areas that are cavernous in structure.

Henzel *et al.*[15] attempted to outline some features which will permit differentiation between the three types (*Table 1*). Two entries listed in *Table 1* warrant emphasis: (1) only cavernous and cystic lymphangiomas have been found in the retroperitoneum, and (2) only in the cavernous and cystic types does lymphangiomatous malignant degeneration occur.

Lymphangiomas most commonly manifest themselves in the neck (75 per cent), when they are called cystic hygromas. The rest are found mainly in the axillary region (20 per cent), while the remaining 5 per cent may appear at various sites in the body, among which are mediastinum[37,38], lungs[39], chest wall, arms, back, parotid, spleen[40–42], liver[43], uterus[44], rectum[45], inguinal region[46], and multiple other sites[33]. Skeletal involvement may be seen as part of a generalized lymphangiomatosis[43,47,48]. In the spleen[49], as in the stomach and omentum[50], the lymphangioma may be associated with intramural gastric pancreas. It may also be found in the oesophagus and stomach[51,52] and in the jejunum[53].

Less than 1 per cent of lymphangiomas are found in the retroperitoneum, those occurring in the mesentery and omentum being called mesenteric and omental cysts, respectively[21,22,33,34,47,54]. Most unilocular lymphangiomas are localized within the mesentery or the omentum, whereas

Table 1 *Differential features in the gross and microscopic characteristics of lymphangiomas (according to Henzel* et al.[15]*)*

	Simple	Cavernous	Cystic
Anatomical location	Skin and subcutaneous tissue of face and neck	Cheek, tongue, buccal tissue, neck, retroperitoneal	Neck (hygroma), axillae, inguinal area, retroperitoneal
Compressibility (patent to adjacent normal lymph flow)	Yes	Yes	No
Unilocular/multilocular	Unilocular	Both	Both
Serous and chylous variants	No	Yes	Yes
Origin congenital	Yes	Yes	Yes
Encapsulated	No	No	No
Microscopic dilated lymphatic spaces	+	++	++ to +++
Endothelial lining within spaces	Yes	Irregularly occurring	Irregularly occurring
Inflammatory cell infiltration	Insignificant	++	++ to +++
Smooth muscle component	Very infrequent	Yes	Yes
Frequency of foam cell	No	+	++
Benign growth	Slow, if at all	Yes	Yes
Potential for malignant transformation	Unknown	Rare but substantiated	Possible

+, Mild, ++, moderate, +++, substantial

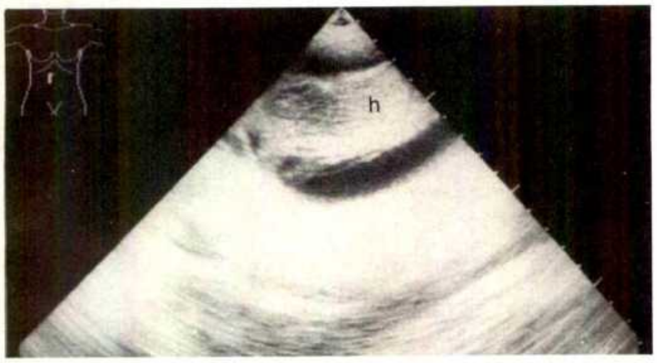

Figure 1 *Real-time ultrasound image showing a portion of the large cystic loculated mass situated in the left upper abdomen with an echogenic structure within the lesion representing the intracystic haemorrhage (h)*

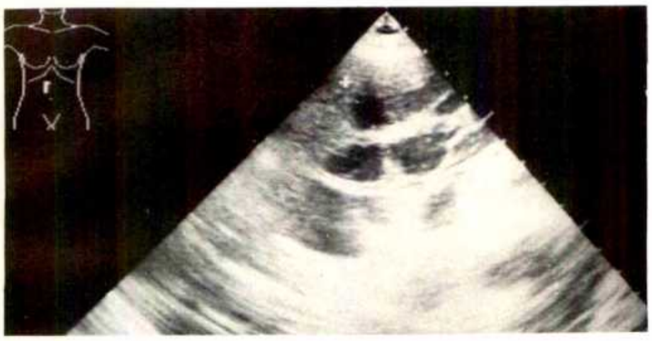

Figure 2 *Real-time ultrasound image showing smaller cystic areas situated in the epigastric region which were part of the large multiloculated mass*

the multiloculated variant may occupy the entire bowel, mesentery and much of the retroperitoneal space.

Clinical features

Retroperitoneal cystic lymphangiomas usually appear in early infancy with about 90 per cent being detected in the first 2 years of life[35]. Except for the series of Takiff *et al.*[25] no sex predilection has been observed. These authors describe 28 patients, eight of whom had cystic lymphangiomas and 20 of whom had mesenteric cysts. Of the eight cystic lymphangioma patients, six were symptomatic; four of the eight patients were found on examination to have ascites and large lesions (mean diameter 8·8cm). Of the 20 patients with mesenteric cysts, six were male, and only five of the entire group of 20 were symptomatic. None of them had ascites, and the lesions were smaller than in the group with lymphangiomas (mean diameter 4·7 cm). There were no clinical features which served to differentiate retroperitoneal lymphangioma from other retroperitoneal masses.

The most common clinical manifestation of retroperitoneal cystic lymphangioma is that of a palpable, soft, cystic mass in the abdomen, which usually enlarges slowly. Some patients may complain of a 'dragging' sensation[15], while others may be asymptomatic, the mass being discovered only incidentally during examination for an unrelated complaint. Like most retroperitoneal masses, these, too, remain occult until pressure occurs, or the mass has become visible or palpable. Pressure symptoms depend largely on the location of the cystic mass, and in 40 per cent of cases pressure on the adjacent structures may cause partial intestinal obstruction[15], displacement of kidneys and ureters to the midline[31], ureteric obstruction[30,55] and displacement of the middle colic artery[56].

The cyst seldom causes acute clinical symptoms and, as the retroperitoneum is relatively inaccessible to physical examination, the diagnosis is often entirely accidental. When acute symptoms do occur, they are due either to pressure on the adjacent structures by the enlarging mass, or to complications, such as haemorrhage into the cyst, inflammation of the cyst wall, infection, perforation, torsion and rupture[17,57,58]. The patient may suffer from abdominal pains and tenderness with guarding and fever; leukocytosis may be present. These cases of acute clinical abdomen may mimic appendicitis, as occurred in 12 per cent of the patients reviewed by Galifer *et al.*[59].

In our own practice we have treated a 25-year-old woman with a large upper mid-abdominal cystic multiloculated mass (*Figures 1* and *2*), and a 20-year-old woman with mesenteric cystic lymphangioma (*Figure 3*). Both patients presented with abdominal pain and fever (38°C) and complained of vomiting. On physical examination, psoas and Rovsing's signs were positive. They underwent laparotomy and excision of the cysts. *Figures 4* and *5* demonstrate the histological findings in these two patients.

Most of the cases reported in children also mention an acute surgical abdomen[37,54,60]. Coagulation disorders described in lymphangiomatosis[39] included features of consumptive coagulopathy[61].

A useful list of conditions to be considered in the differential diagnosis of lymphangioma has been compiled by Blumhagen *et al.*[62] (*Table 2*).

Radiographic findings

Previously, the diagnosis of lymphangioma was made during surgery or at autopsy. Currently, we have access to methods

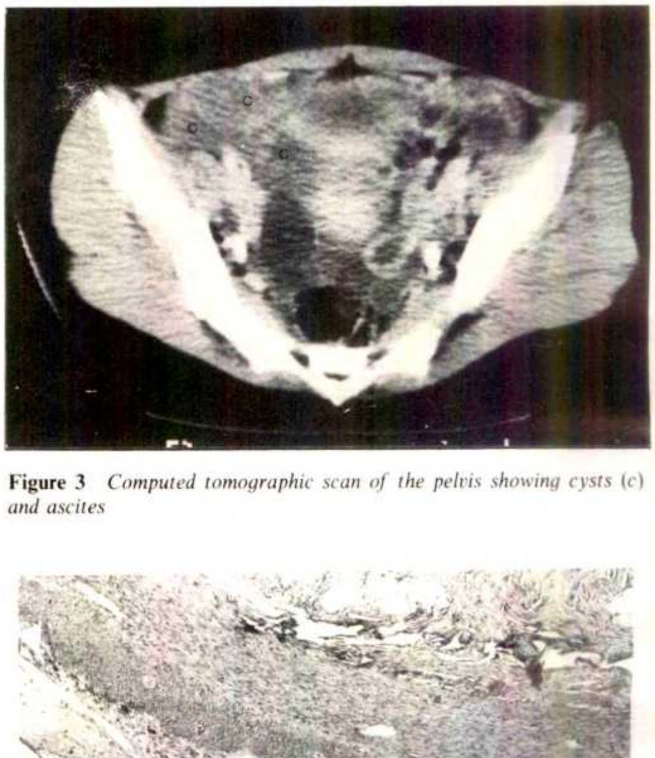

Figure 3 *Computed tomographic scan of the pelvis showing cysts (c) and ascites*

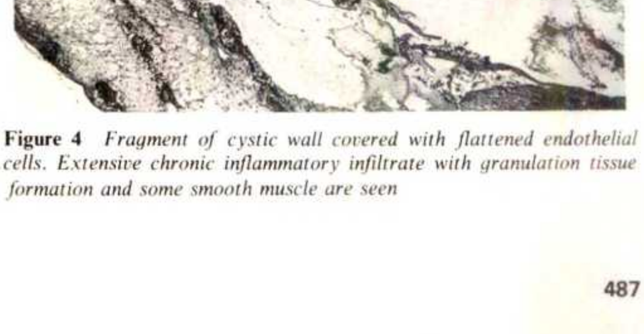

Figure 4 *Fragment of cystic wall covered with flattened endothelial cells. Extensive chronic inflammatory infiltrate with granulation tissue formation and some smooth muscle are seen*

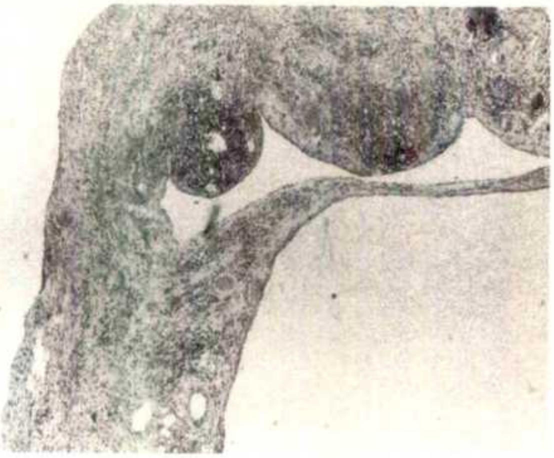

Figure 5 *Cystic lymphangiectasis beneath the serosal surface of the appendix*

Table 2 *Differential diagnosis of lymphangioma (according to Blumhagen* et al.[62])

- Huge lesions
  - Ovarian:
    - Teratoma
    - Cystadenoma
    - Mucinous cystadenoma
  - Pancreatic pseudocyst
  - Multilocular cystic nephroma
  - Lymphoma (not truly cystic)
- Lesions of moderate size
  - Haematoma
  - Postoperative seroma
  - Peritonitis
  - Echinococcal cyst
  - Enteric duplication
  - Lymphoma (not truly cystic)
  - Kidney:
    - Polycystic kidney disease
    - Cystic dysplasia
    - Clear cell sarcoma
  - Spleen:
    - Epidermoid cyst
  - Liver:
    - Mesenchymal hamartoma
    - Cystic hepatoblastoma
    - Haemangioendothelioma
    - Choledochal cyst
    - Carolis disease
    - Embryonal sarcoma

of imaging that afford a preoperative diagnosis. Radiographs may be helpful in localization through displacement of surrounding viscera, and calcification has been described in a cavernous pancreatic lymphangioma[63]. Asch *et al.*[43] reported on a calcified cystic lesion in the spleen of a child with diffuse involvement of the liver.

Intravenous urography may be of value in revealing displacement of the kidney or ureters. A barium enema may demonstrate medial or lateral displacement of the ascending or descending colon without obstruction, while barium studies of the duodenum may assist in the diagnosis of a lymphangioma arising in the upper abdomen.

Other diagnostic imaging methods have proved of value in preoperative localization of these masses and in defining their internal architecture. Ultrasound contributes to the diagnosis of lymphangioma by showing a cystic mass with multiple thin septa. This mode of examination also shows the relationship of the mass to abdominal and retroperitoneal structures[62].

The computerized tomographical features of cystic lymphangiomas are uni- or multilocular massses of water density (*Figure 3*). The wall of the mass may be enhanced following intravenous administration of contrast material. The septa are of uniform thickness[32]. In one case, the computed tomograpical attenuation of 15 Hounsfield units within the cyst suggested the presence of fat within the lesion[34].

Although the efficacy of magnetic resonance imaging in displaying the cystic lesion is comparable to that of computed tomography, the signal intensities and T-1 and T-2 values, which differ between cysts, may reflect differences in the composition of cystic fluids[30].

With lymphangiography, only those lymphangiomas that communicate with the lymphatic system are directly visualized. A cystic lymphangioma of the mesentery (mesenteric cyst), which was shown to communicate with the thoracic duct, demonstrated dilatation of interconnecting lymphatic channels with passage of contrasting material into the mesenteric cystic spaces on lower extremity lymphangiography[64].

Angiography clarifies the manner in which the mass causes displacement of arterial branches, as well as stretching of an artery by the tumour, although the method does not show tumour vascularity.

Of the methods noted here in brief we advocate ultrasound and computed tomography as the most efficacious procedures for visualizing abdominal lymphangiomas.

Treatment

Complete excision is the treatment of choice and it is usually carried out with relative ease. Aspiration of the larger cysts lessens the difficulty with exposure. If the cyst has invaded an abdominal organ like the small bowel, spleen or the tail of the pancreas[25], total excision with resection of the involved organ is indicated. In the past, both external and internal marsupialization were performed. Although cystenterostomy has been suggested, the form of drainage preferred was internal peritoneal cavity marsupialization. Such surgical forms of treatment have become obsolete, and the modern approach advocates total excision of the mass in a patient with cystic retroperitoneal lymphangioma. With incomplete removal of the cyst, there is a possibility of recurrence at a later date, such as was observed by Raszkowski *et al.*[65] 7 years after the original surgical intervention.

Conclusions

The historical review demonstrates the relative rarity of cystic abdominal lymphangioma. The aetiology of the lesion is probably a primary malformation of the lymphatic system, essentially a hamartoma, which may either grow continuously, or cause blockage and subsequent enlargement of lymphatic channels.

Histologically, lymphangiomas can be distinguished into simple, cavernous and cystic types. The clinical features are typically those of a space-occupying lesion causing pressure on adjacent structures or of complications within the lesion itself. The patient often presents with an acute surgical abdomen. Ultrasound is the imaging modality of choice, owing to the cystic internal consistency. Other imaging modalities, especially computerized tomography, may be useful. The recommended treatment is complete excision.

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Gastric banding in the treatment of morbid obesity

R. M. Kirby, T. Ismail, M. Crowson and R. M. Baddeley

Department of Surgery, General Hospital, Steelhouse Lane, Birmingham, B4 6NH, UK

Correspondence to:
Mr R. M. Baddeley

Gastric banding was carried out in 30 patients as a treatment for morbid obesity. The mean excess weight lost at 3 months was 32·6 per cent (27 patients) and 69·7 per cent at 2 years (eight patients). Fifteen patients required 22 reoperations for technical complications. Two patients underwent removal of the band and seven patients were converted to a stapled vertical Silastic® ring gastroplasty. Although gastric banding appears to be a satisfactory method of achieving weight loss, the complication and reoperation rates are unacceptable in our hands. It is recommended that this operation should no longer be used as a treatment for morbid obesity.

Keywords: Morbid obesity, gastric banding, weight loss, complications

Bariatric surgery, the surgery of morbid obesity, has been revolutionized by the introduction of gastroplasties. These procedures have been pioneered by Gomez[1] using the horizontal gastroplasty and Mason *et al.*[2] using the vertical banded gastroplasty. Other techniques, e.g. gastric partitioning with gastrogastrostomy and gastric partitioning with removal of staples to create a stoma[3], have failed to achieve satisfactory long-term results. We have randomly compared two groups of patients undergoing vertical Silastic® (Dow Corning, Reading, UK) ring gastroplasty and horizontal gastroplasty and found that, although good weight reduction was achieved with both, the reoperation rate was high with horizontal gastroplasty and this technique was subsequently abandoned[4]. An alternative gastroplasty, gastric banding (the separation of the stomach into two compartments by a band passed around the upper part of the stomach) has been reported to be a simple, cheap and effective form of gastroplasty. A small trial was therefore commenced in 1985 and our experience is reported here.

Patients and methods

After investigations to exclude endocrine abnormalities and other causes of obesity, and after psychological assessment, 30 patients referred for treatment of morbid obesity were assigned to the trial of gastric banding. The majority were women (male:female ratio 5:25). The mean age was 37·7 years (range 24–54 years). The mean weight of the patients was 134·7 ± 30·4 kg and the mean body mass index (weight in kilograms/height in metres^2) was 50·8 ± 9·1.

All operations were carried out by one surgeon (R.M.B.). Laparotomy was performed through an upper abdominal midline incision with the table tilted 45° (foot down). After minimal dissection of the lesser curvature and fundus a Dacron® or Teflon® (E.I. du Pont de Nemours and Company, UK) band was passed around the upper part of the stomach, tightened and sutured into place to provide a 50-ml proximal compartment and a 1·2-cm diameter stoma into the distal stomach[1,5]. The proximal and distal compartments were sutured to each other, lateral to the band, to prevent it from slipping (*Figure 1*). Postoperatively the patients were commenced on an 800-calorie liquid diet and converted to solid food at 6 weeks.

Patients were followed up at 1 month and then at 3-monthly intervals after operation. They were assessed objectively by the measurement of the weight loss and the representative percentage of excess weight lost based upon Metropolitan Life Assurance tables[12] and reduction of mean body mass index. Not having available an objective method of assessing proximal compartment volume, a crude subjective guide was obtained by asking each patient to estimate whether the size of meals that she or he could eat could be served on a saucer, tea plate, dessert or dinner plate. Haematological and biochemical parameters were checked at each visit.

Results

Patients were followed up for between 6 months and 2 years. Two patients had the banding reversed 7 and 19 months after initial surgery. A further seven patients were converted to vertical gastroplasties at a mean of 17 months (range 10–25 months, see below) and seven were lost to follow-up. Nineteen patients would have been eligible for follow-up at 2 years although only eight could finally be assessed after non-attenders (five) and those being reversed or converted (six) were removed.

Weight loss

One patient was withdrawn from the study because during operation the upper stomach could not be fully visualized owing to the grossly excessive obesity (223·6 kg). Although gastric banding was carried out, the size of the proximal compartment was not fully controlled. His weight loss was minimal, with only 13·4 per cent of his excess weight being lost after 2 years.

The loss of excess weight and reduction of body mass index (weight in kilograms/height in metres^2) of the remaining patients are outlined in *Tables 1* and *2*. It can be seen that the majority of weight was lost in the first 12 months, although it continued for 18 or 24 months in some.

Subjective pouch assessment (Figure 2)

Twenty-four patients assessed the size of their meals at 3 months and ten at 2 years (this included a patient who was not included in the weight assessment, and a non-attender who was quizzed by telephone but was unable to give her present weight).

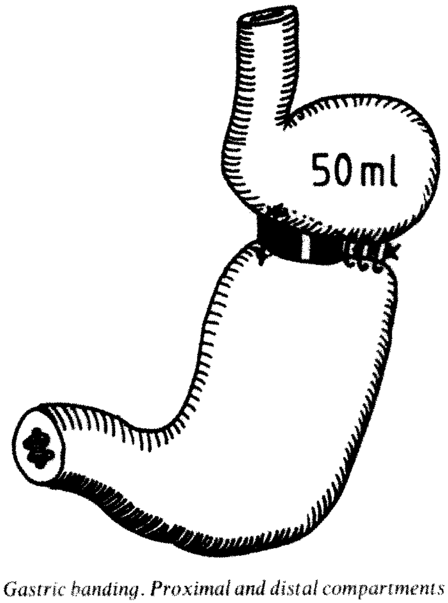

Figure 1 *Gastric banding. Proximal and distal compartments are sutured to each other lateral to the band to prevent it from slipping*

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Table 1. *Percentage of excess weight lost*

Time (months)	No. of patients	Mean	Standard deviation	Minimum	Maximum
3	27	32·6	12·2	6·4	54·5
6	25	49·7	15·6	25·4	85·4
12	23	54·4	24·4	0	96·5
18	16	60·2	32·8	4·7	129·5
24	8	69·7	27·7	20·7	103·0

Table 2 *Changes in mean body mass index*

Time (months)	No. of patients	Mean	Standard deviation
Before operation	29	50·8	9·1
3	27	43·1	9·1
6	25	38·8	9·2
12	23	37·5	9·8
18	16	35·0	8·8
24	8	36·8	12·3

Body mass index = weight in kilograms/height in metres^2

Thirteen of the original 24 patients were able to eat only a saucer-sized meal 3 months after operation, whereas only one of the final ten patients was eating meals this small. Seven of these patients had noticed an increase in pouch size, although only three of them had been taking saucer-sized meals initially. Eighteen patients in total noticed an increase in the size of meals they could take. Two patients reported a decrease in meal size and five did not report any change. (One patient missed the 3-month assessment.)

Complications and reoperation

There were no deaths as a result of surgery and no later deaths. Seventeen patients required reoperation but two of these were for cosmetic reasons (abdominal apronectomy) and were, therefore, not considered further. Of the remaining 15 patients, two had three reoperations and three had two reoperations, giving a total of 22 reoperations.

Four patients required surgery because the band was too tight. Two patients simply had the bands removed because of severe vomiting, one of them occurring a month after reoperation for intussusception (see below). One patient had the banding revised and one had the banding converted to a vertical stapled Silastic® ring gastroplasty.

Seven patients required further surgery because the banding was too loose or ineffective. The banding was revised in five patients, and converted to a vertical gastroplasty in three. One patient in the latter group had two operations.

Four patients developed an intussusception of the distal gastric compartment into the proximal. Barium meal radiographs had suggested volvulus at the site of the band, although there was no evidence of this at reoperation. The banding was simply revised in three patients but was converted to a stapled gastroplasty in two of these patients and in the fourth patient. Two of the latter patients were those undergoing three reoperations: two reoperations in each case were for intussusception. One of the patients simply undergoing revision needed to have the band removed 1 month later because of extreme vomiting.

Four patients required reoperation for more conventional surgical complications. There were three ventral hernias which required repair and one patient needed a laparotomy for division of adhesions.

Discussion

This is a small study in comparison with other international programmes. The assessment was made more difficult by the poor compliance with follow-up which resulted in 23 per cent of the group being lost to follow-up. It could be assumed that those patients absconding were treatment failures, although two had achieved a satisfactory excess weight loss (> 65 per cent) at the last attendance.

Rao[6] has reported 240 cases of gastric banding with a weight loss of 35–40 kg at the end of 12 months (mean weight 140 kg, 58 kg excess). By the third year 20 per cent started to regain weight and 10 per cent continued their weight loss. He used a silicone rubber-coated Dacron ring and has found a lower complication rate than we have. Kuzmak[7] has reported the use of an inflatable Silastic band in 45 patients with a resultant 53·5 per cent weight loss at 6 months. Lovig *et al.*[8] used a Dacron vascular prosthesis as a band and achieved a mean weight loss of 33·4 kg (27·6 ± 1·9 per cent) at 2 years in 163 patients. Serious complications occurred in ten patients and required reoperation, with one death. The band penetrated the gastric wall in three others. Our use of Dacron or Teflon bands probably induced a degree of fibrosis and may have been responsible for kinking of the stoma by adhesions to the liver. The ease with which they could be removed suggests that they were not a cause of stenosis. The results from this study suggest that the weight loss as a consequence of the operation is satisfactory, with an increasing weight loss at 2 years. Even if weight loss settles after 2 years, a loss of 70 per cent of excess weight is good. Before analysis of the results of this study it was suspected that the results would mirror those of the horizontal banded gastroplasty. Both these procedures include the fundus in the gastroplasty. Unlike the vertical gastroplasty, this then allows room for expansion. This is almost certainly the reason for the subjective increase in pouch size which has been demonstrated. An objective assessment using barium or radioisotope studies would have given more accurate assessment of pouch size[9], but our method allows patient compliance and gives at least an indication of meal size.

Technical difficulties with the gastric banding procedures focus on the tightness of the band in achieving an accurate 1·2 cm stoma diameter. When the band was too loose, gastric emptying occurred too rapidly and the patients resumed eating to satisfy hunger. Too tight a band resulted in dilatation of the proximal compartment and increased capacity with or without vomiting. Patients tended to eat to capacity, usually with poor quality high-calorie foods, and weight loss became impaired. Kuzmak[10] has used a pressure measurement of the band on

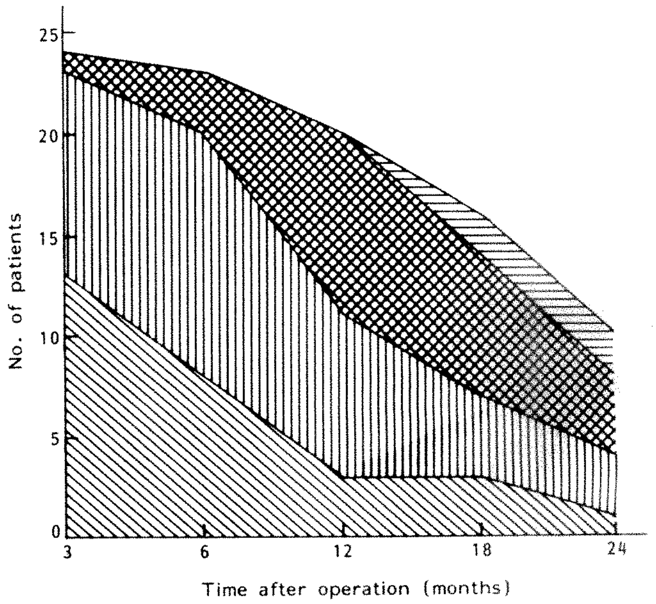

Figure 2 *Subjective assessment of pouch size. Patients estimated whether the size of meals they could eat could be served on a saucer ▧, a tea plate ▥, a dessert plate ▩, or a dinner plate ▤*

a tube passed through the stoma and by using this inflatable silicone band would appear to have best control over the stoma dimension.

If the achieved weight loss was taken in isolation the operation could be said to be successful. We have reported an extremely high rate of complications with 50 per cent of patients requiring at least one reoperation and 22 reoperations for technical complications. Four patients (13 per cent) had bandings that were too tight whereas banding was too loose in six patients (20 per cent). Perhaps use of an inflatable band would have altered these results, although adhesion formation is unlikely to allow a tight band to relax sufficiently. It is interesting to postulate the cause of intussusception in four patients, which was recurrent in two, even after two reoperations. It was probably a result of vomiting with reverse peristalsis forcing the distal compartment through the stoma. A simple revision was attempted in three patients for this condition, but conversion or removal subsequently became necessary for all three patients.

Similar technical difficulties were reported by Grandström and Backman[11] in a series of 72 patients. One-third of the patients had serious complications. Thirty-three reoperations were performed in 22 patients due to band-related problems, with two deaths. Only three revision procedures achieved a satisfactory result. Reduction in band tension gave fewer revisions but also less weight loss.

Gastric banding was introduced as an easy and cheap alternative gastroplasty. One of the reported benefits of the procedure is the ease of reversibility. Simple reversal only needed to be carried out in two of our patients but reversal plus conversion to vertical Silastic ring gastroplasty was necessary in seven further patients. This represents a 30 per cent rate of reversal and/or conversion which would appear to be an unacceptable rate of complications. We have therefore discontinued gastric banding gastroplasty as a method of treatment for morbid obesity, preferring the vertical Silastic ring gastroplasty on the basis of earlier experience in more than 100 patients using this procedure.

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Continuous single-layer gastrointestinal anastomosis: a prospective audit

S. Sarin and
R. G. Lightwood

Department of Surgery,
East Surrey Hospital,
Three Arch Road, Redhill,
Surrey RH1 5RH, UK
Correspondence to:
Mr R. G. Lightwood

Single-layer bowel anastomoses have conventionally been constructed using an interrupted suture technique. A single-layer continuous technique has been avoided on the grounds that it may predispose to ischaemia of the bowel ends. We have routinely used a single-layer continuous suture technique with an absorbable suture material (polyglycolic acid) to construct all recent intraperitoneal bowel anastomoses, and we present a 3-year audit of this technique. A total of 131 patients were studied of whom 66 had undergone upper gastrointestinal resections and 65 had had colonic resections. Twenty-two patients had emergency operations. Anastomotic failure was noted in 4·5 and 6·2 per cent of patients in each group respectively. The incidence of minor wound infection was 1·5 and 7·7 per cent respectively. The overall mortality rate was 8·4 per cent. This study suggests that a single-layer continuous suture technique gives acceptably reliable results when used in gastrointestinal anastomosis.

Keywords: Colon anastomosis, polyglycolic acid

Anastomotic breakdown remains a major cause of morbidity and mortality after operations on the gastrointestinal tract. Colonic anastomoses are particularly liable to this complication. A recent large multicentre series reported an average clinical anastomotic dehiscence rate of 13 per cent with an associated three-fold increase in perioperative mortality following colonic resection[1]. Lack of suture line tension, effective bowel preparation, avoidance of ischaemia and infection, an inverting suture technique and omental overlay form the basis of a sound anastomosis[2–6]. Conventionally, an anastomosis is constructed in two layers comprising an inner continuous suture (such as catgut) and an outer interrupted seromuscular suture (such as silk). Recently, avoidance of the inner 'haemostatic' layer, on the grounds that it may compromise an already precarious blood supply, has resulted in a number of series in which the anastomoses have been constructed safely using single-layer interrupted suture techniques[5–9]. A single-layer continuous technique has always been avoided on the same premise. However, one of us (R.G.L.) has long used a simple, single-layer, continuous suture technique with an absorbable suture material (polyglycolic acid) for the construction of all intraperitoneal gastrointestinal anastomoses with apparent success; a prospective audit was therefore undertaken.

Patients and methods

All patients undergoing intraperitoneal bowel anastomoses during a 3-year period between January 1984 and February 1987 were studied. The patients were admitted under the care of the senior author (R.G.L.) who undertook all operative procedures. Data on each consecutive patient were collected during their stay in hospital and at subsequent follow-up. There was a total of 131 patients (78 men and 53 women) with a mean age of 64·3 ± 13·9 years (range 19–91 years). They were divided into two broad groups: those undergoing upper gastrointestinal anastomoses (gastric, biliary, duodenal and small bowel) and those undergoing lower gastrointestinal anastomoses (colonic). There were 66 patients in the upper gastrointestinal group (41 men and 25 women) and 65 patients in the lower gastrointestinal group (37 men and 28 women). *Tables 1* and *2* show the indications for resection and the operations involved.

There was a total of 22 emergency procedures. Five patients underwent gastric resection for bleeding peptic ulcer. Nine patients had small bowel resections for strangulation due to adhesions or hernias. Five patients underwent a right hemicolectomy, two as a result of infarction in the superior mesenteric artery territory and three secondary to obstructing carcinoma of the colon. One patient had an ileocolic bypass because of an unresectable carcinoma of the caecum. Two additional patients required left colonic resections, one for a sigmoid volvulus and the other for an obstructing carcinoma of the sigmoid colon. This last procedure was the only one 'covered' by a defunctioning colostomy.

Preoperative preparation and antibiotics

All patients having elective surgery involving a colonic anastomosis were restricted to fluids for 48 h preoperatively. Bowel preparation was achieved by sodium picosulphate, 10 mg (one sachet) at 24 h and at 18 h before operation. Gentamicin and metronidazole were used in preparation for colonic procedures and cefuroxime for upper gastrointestinal procedures; the antibiotics were given at induction of anaesthesia and continued for 24 h after the procedure. No special preoperative preparation was used for patients undergoing upper gastrointestinal anastomoses.

Table 1 *Indications for surgery in 131 patients undergoing intraperitoneal bowel anastomoses*

Indication	No. of patients
Upper gastrointestinal tract	
Carcinoma of the stomach	23
Carcinoma of the pancreas	18
Peptic ulceration	7
Leiomyoma	2
Carcinoid	2
Ampullary carcinoma	2
Strangulated hernias	5
Adhesions	4
Others	3
Lower gastrointestinal tract	
Carcinoma of the colon	52
Colonic adenoma	3
Superior mesenteric artery infarction	2
Diverticular disease	4
Crohn's disease	1
Sigmoid volvulus	1
Endometriosis	1
Tuberculosis	1
Total	131

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Table 2 *Operations performed and their outcome*

	Emergency surgery			Elective surgery		
	No. of operations	No. of leaks	No. of deaths	No. of operations	No. of leaks	No. of deaths
Upper gastrointestinal tract						
Partial gastrectomy	3	—	—	23	1	1
Gastrojejunostomy	—	—	—	9	—	1
Cholecystjejunostomy	—	—	—	6	—	—
Gastrojejunostomy + cholecystjejunostomy	—	—	—	8	1	3
Small bowel resection	9	1	1	4	—	—
Others	2	—	1	2	—	—
Total	14	1	2	52	2	5
Lower gastrointestinal tract						
Right hemicolectomy	5	2	1	19	2	1
Left hemicolectomy	2	—	—	22	—	1
Anterior resection	—	—	—	8	—	1
Ileocolic bypass	1	—	—	2	—	—
Closure of colostomy	—	—	—	6	—	—
Total	8	2	1	57	2	3

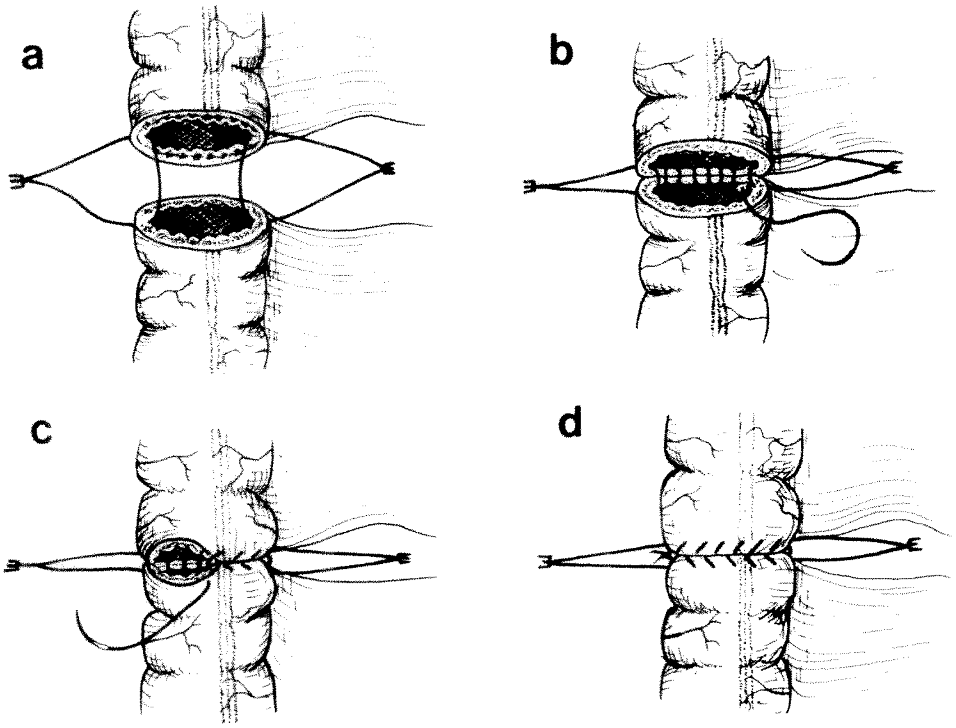

Figure 1 *Diagrams showing a colonic anastomosis:* **a** *insertion of 2/0 polyglycolic acid stay sutures;* **b** *posterior layer constructed using an 'over and over' full thickness stitch starting at the antimesenteric border;* **c** *anterior layer of the anastomosis formed by using an 'in out, in out' full thickness stitch;* **d** *final anastomosis showing completed anterior layer*

Operative technique (Figure 1)

Colonic anastomosis. The bowel wall was not extensively 'cleaned' at the site of proposed section. Non-crushing clamps were placed across the bowel approximately 5 cm from the line of resection taking care not to include the mesentery in the ends of the clamps. Bowel was divided between two crushing clamps. Two full thickness polyglycolic acid sutures were inserted, one at the mesenteric border and one at the antimesenteric border to approximate the bowel ends. The anastomosis was constructed with 2/0 polyglycolic acid using a continuous suture technique. The anastomosis was started at the antimesenteric border and run along using a simple 'over and over' full thickness stitch to form the posterior layer. At the mesenteric edge two Connell stitches ensured inversion of the corner and the stitch was continued 'in out, in out' to form the anterior wall and meet itself at the start of the anastomosis at the antimesenteric border. Care was taken to pull the suture tightly enough just to approximate the bowel edges and also to ensure that the bowel wall was inverted. The stay sutures were removed and the mesenteric defect was closed using 2/0 polyglycolic acid in a continuous manner. Omentum, if available, was laid over the anastomosis. All anastomoses were performed end-to-end except for the three ileocolic bypass procedures. Gross bowel disparity was corrected using an antimesenteric 'slit'. Drainage was used only for raw peritoneal surfaces.

Other anastomoses. Gastrojejunostomies and cholecystjejunostomies were constructed side-to-side in a manner similar to that used in ileocolic anastomoses. The use of clamps was kept to a minimum. Nasogastric tubes were used routinely in patients having gastric anastomoses.

Postoperative care

All patients remained on intravenous fluids with no oral intake until evidence of gastrointestinal motility was present (reduced drainage from the nasogastric tube, bowel sounds and passage of flatus). Fluids were then given orally in gradually increasing amounts and food was started 48 h later. Abdominal drains, if used, were usually removed between 48 and 72 h after the procedure. The abdominal wounds were assessed during the in-patient stay and also at the first out-patient follow-up appointment (approximately 4 weeks after discharge).

Results

Upper gastrointestinal tract

Three patients (4 per cent) had evidence of anastomotic dehiscence. Two of these three patients developed peritonitis 7 and 8 days postoperatively, one patient after a subtotal gastrectomy for an obstructing carcinoma of the stomach (confirmed radiologically) and the other after a cholecystjejunostomy for carcinoma of the pancreas (diagnosed clinically). Both of these patients died as a result of the anastomotic dehiscence. The third patient developed an intestinal fistula 8 days after an emergency resection of small bowel secondary to strangulation by adhesions.

Overall, seven patients (11 per cent) died in this group. Two deaths were considered to be secondary to anastomotic failure; the others followed myocardial infarction (one death), pulmonary embolism (one death), renal failure (one death) and bronchopneumonia (two deaths). One patient developed a pancreatic fistula following open pancreatic biopsy. The incidence of overt wound infection was 1·5 per cent.

Lower gastrointestinal tract

Four patients (6 per cent) developed evidence of intra-abdominal sepsis, which was treated conservatively. All had undergone right colonic resections, two of which were emergency operations. Two of these four patients died, one after a limited right hemicolectomy for disseminated carcinoma of the colon and the other after an extensive emergency resection for a superior mesenteric artery infarct.

Four patients in this group died (6 per cent), two patients dying secondary to anastomotic dehiscence and two others following myocardial infarction. Five patients (8 per cent) developed minor wound infections.

Discussion

The frequency of suspected anastomotic dehiscence following right colonic procedures may reflect a number of factors. Six of the 27 right colonic procedures were undertaken on an emergency basis and two of these six patients developed evidence of anastomotic failure. Both had undergone resection with primary anastomosis secondary to infarction in the superior mesenteric artery territory. Recent literature would suggest that primary anastomosis may not be appropriate in these cases despite seemingly viable bowel ends at operation. Also an assumption of the 'good' healing properties of the right colon may lead to an increased tendency to perform a primary anastomosis in spite of other relative contraindications[10].

All four patients with evidence of intra-abdominal sepsis following colonic anastomosis were treated conservatively on clinical grounds. Debas and Thomson[10] advocate an active interventional approach in the treatment of suspected anastomotic failure. Though appropriate in most situations, we feel that in some instances this view may be difficult to justify. For example, where an initial palliative procedure had been undertaken for disseminated malignancy our policy was to treat patients with intra-abdominal sepsis conservatively.

Whether the suture material used in the construction of gastrointestinal anastomoses affects outcome to a significant degree is doubtful, as demonstrated by the variety of materials used in many reported clinical series[1–9]. Ideally the suture should remain 'available' while the bowel is healing and should be completely absorbed after this process is complete. Materials that produce an excessive reaction may predispose to infection and are liable to cut out[8]. Catgut produces an intense reaction and has an unpredictable absorption rate. Silk is non-absorbable and also produces an excessive inflammatory reaction[11]. Non-absorbable synthetic materials, although inert, are foreign bodies. A number of clinical and experimental studies suggest that polyglycolic acid may be a suitable alternative[9,12–14]. However, a possible disadvantage is its braided nature which may allow infection to be harboured and which may produce mechanical damage as a result of a 'sawing' action as the suture is pulled through the tissue. We are currently assessing the use of a synthetic monofilament absorbable suture material in the construction of gastrointestinal anastomoses.

The issue of whether to have a one- or two-layer anastomosis seems as yet unresolved. Theoretically, two-layer anastomoses may predispose to ischaemia of the bowel ends[12] and reduce the lumen of the bowel[3], and there is some experimental evidence to suggest that a conventional two-layer anastomosis may not remain as two layers for very long[11]. One-layer interrupted anastomoses have been shown to be satisfactory in a number of clinical series[5–9] despite being constructed with a variety of suture techniques and suture materials.

We conclude that, in our hands, there appears to be no disadvantage in using a single-layer continuous suture technique with a slowly absorbable suture material in the construction of intraperitoneal gastrointestinal anastomoses. We suggest further that the theoretical risk of ischaemia incurred by using this technique is not substantiated in practice.

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Use of a bioprosthesis to relieve tension in oesophageal anastomosis: an experimental study

Collagen-coated Vicryl® mesh was assessed as a prosthetic repair material in the oesophagus of growing piglets. In a group of six piglets (group A), a full thickness defect was created in the oesophagus without fully transecting the organ. The removed tissue was subsequently replaced with a patch of collagen-coated Vicryl mesh. Animals were killed at 4 weeks and in the five surviving piglets the prosthesis had been replaced by host scar tissue with a normal epithelial lining. Two further groups of six piglets (groups B and C) were used as controls. In group B the oesophagus was either partly transected (four animals) or completely transected (two animals) and an anastomosis was performed, whereas in group C a 2·5-cm length of oesophagus was removed so that the anastomosis was performed under tension. In group B, all six piglets survived, whereas in group C, where the anastomosis was performed under tension, only two piglets survived. Microscopic and macroscopic examination of all groups showed that the collagen-coated Vicryl prosthesis was replaced by scar tissue; moderate stenosis was observed in only one animal in group A. Collagen-coated Vicryl mesh may be used either to reinforce an anastomosis performed under tension or may find use in tubular form to bridge the gap between the two ends of the oesophagus to be joined. It is envisaged that such a material may find applications in the treatment of oesophageal atresia.

Keywords: Oesophageal anastomosis, tension, bioprosthesis

R. Carachi, A. Azmy, S. Gorham, J. Reid and D. A. French

Department of Paediatric Surgery, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ, UK

Correspondence to:
Mr R. Carachi

The outcome for infants with oesophageal atresia primarily depends on the number and importance of the associated anomalies. Irrespective of an infant's birth-weight, a 95 per cent survival rate in babies with oesophageal atresia without other major anomalies is obtained. The high incidence of other major anomalies decreases the overall survival rate of infants with oesophageal atresia to approximately 75 per cent[1]. There still remains a significant clinical problem of leaks at the site of oesophageal anastomosis, resulting in stenosis. Other recognized problems with this operation are tension, infection, foreign material, such as suture material, and ischaemia at the anastomotic site[2].

To investigate the complications at the site of anastomosis, several experimental studies have been carried out using a variety of techniques. These have involved the use of various types of oesophageal stents and transanastomotic tubes[3,4] but there remains a requirement for some method of reducing tension at the anastomosis. The use of a prosthetic patch at an anastomosis has been tested as a way of preventing tension as well as of sealing any leaks at the anastomotic site. Vicryl® (Ethicon Ltd., Edinburgh, UK) (polyglactin 910) is a copolymer of glycolic and lactic acids containing 90 and 100 per cent of each component respectively. It is a water-soluble polymer used in the manufacture of surgical sutures but, when woven into a mesh it has also found encouraging application in tissue augmentation[5]. It was envisaged that such a mesh when made leakproof with a biodegradable film such as collagen may well provide a useful prosthetic material for reinforcing an anastomosis performed in the oesophagus. Indeed, such a composite has already shown considerable potential in the repair of the urinary tract, where it has been used to augment an experimental defect created in the bladder[6], and in partial nephrectomy where it has allowed a new capsule to regenerate over the excised kidney[7]. This report describes an experimental study (in piglets) of repair of the oesophagus after transection and excision of part of the oesophageal wall.

Materials and methods

Vicryl® (polyglactin) mesh, style 9, was obtained from Ethnor, Neuilly sur Seine Cedex, France. Collagen-coated Vicryl mesh was prepared by the method of Gorham *et al.*[8]. Piglets 3–4 weeks old were premedicated with atropine, and anaesthesia was induced with halothane in a mixture of nitrous oxide and oxygen. Following intubation, spontaneous respiratory movements were abolished by hyperventilation. Each piglet was positioned for a right-sided thoracotomy and the skin, after clipping, was prepared with povidone (polyvinyl pyrrolidine iodine) and alcohol. An incision was made through skin, fascia (*Figure 1*) and muscle, down to the sixth intercostal space. The pleura was opened and, with the help of a self-retaining retractor to spread the ribs, the lung was retracted. The parietal pleura over the mediastinum was then divided and the oesophagus was

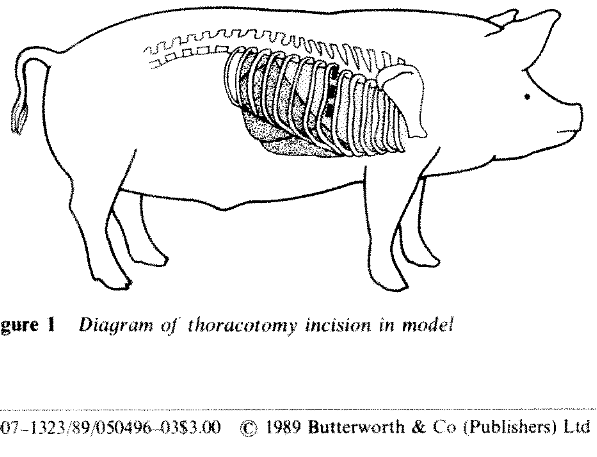

Figure 1 *Diagram of thoracotomy incision in model*

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Table 1 *Weight gains of experimental piglets over 4 weeks*

Group A			Group B			Group C		
Starting weight (kg)	Final weight (kg)	Final weight/ starting weight	Starting weight (kg)	Final weight (kg)	Final weight/ starting weight	Starting weight (kg)	Final weight (kg)	Final weight/ starting weight
8·8	Died	—	8·8	11·0	1·2	12·0	29·5	2·5
9·0	21·5	2·4	16·0	31·0	1·9	17·0	Died	—
9·0	24·0	2·7	7·0	28·6	4·1	19·0	Died	—
10·0	25·0	2·5	7·0	26·6	3·8	10·0	Died	—
10·8	43·0	4·0	6·7	19·8	3·0	11·1	22·6	2·0
10·8	34·0	3·2	7·6	23·4	3·1	30·5	Died	—
		2·9 (0·7)*			2·8 (1·1)*			

* Mean ±s.d.

mobilized taking care to avoid the vagus nerve and segmental blood vessels. A tape sling was passed around the oesophagus once a nasogastric tube had been passed by the anaesthetist. The operative procedure was then performed as follows.

Group A (six piglets). A 2·5-cm elliptical portion of the anterior wall of the midthoracic oesophagus was excised without completely transecting the oesophagus, and the collagen-coated Vicryl mesh patch was sutured in place without tension.

Group B (six piglets). Partial (four animals) or complete (two animals) transection of the oesophagus was performed, followed by anastomosis without tension using 4/0 silk.

Group C (six piglets). The oesophagus was divided and a 2·5-cm section was removed before reanastomosis. The oesophagus was then repaired under tension using 4/0 silk sutures.

The pleura over the oesophagus was closed as a separate layer and the lungs were then gradually reinflated. Pericostal sutures of 2/0 monofilament nylon were used to approximate the ribs. The muscles were closed with a continuous Vicryl suture and the skin was closed with 2/0 Supramid® sutures (B. Braun Melsungen A.G., FRG).

An intercostal chest drain was used to aspirate air from the thorax, and was removed after complete closure of the chest wall.

Postoperative care

Pethidine (2 mg/kg) was administered by intramuscular injection before termination of anaesthesia, and subsequent analgesia was given as required. Prophylactic antibiotic cover consisted of a single dose of long-acting penicillin. The piglets were fed powdered milk *ad libitum* for 72 h postoperatively and then softened feed.

Assessment of stenosis and histology

Animals in all three groups were killed after 4 weeks, weighed, and the oesophagus was removed at post-mortem examination. After death, stenosis at the repair site in all three groups of animals was assessed by first sealing the distal end of the oesophagus by tying with a suture and filling the organ with barium sulphate before X-ray examination. The results were assessed independently by two authors (A.A. and J.R.) without knowledge of the groups. After this assessment of the stenotic area, appropriate sections were fixed in buffered formalin and processed for routine histology, using haematoxylin, phloxine and saffron (HPS trichrome) staining. The barium studies on the oesophagus at post mortem allowed a grading system for the oesophageal anastomosis. Each was graded according to whether they showed minimal stenosis (+), moderate stenosis (+ +) or severe stenosis (+ + +).

Weight gains of group A and group B piglets were compared using the Student's *t* test for unpaired samples.

Results

In group A where piglets had a collagen-coated Vicryl mesh patch, one piglet died from a leak at the oesophageal anastomosis; the remaining five piglets survived and grew as well as the control group B (*Table 1*). All six piglets in control group B survived, whereas all six piglets in group C suffered from mediastinitis. Attempts were undertaken to control this infection at the anastomotic site with broad-spectrum antibiotics, but four of the six piglets died or were destroyed on humane grounds. Two survivors developed respiratory signs at day 3, but responded to treatment. The weight gains of the piglets in group A compared with group B showed no statistically significant difference ($P = 0·8$; *Table 1*). Given that only two piglets survived in group C, there were insufficient data to assess whether the gain in weight over 4 weeks was significantly different from that seen in groups A and B. However, the values lie within the range of the weight gains of group A and B animals.

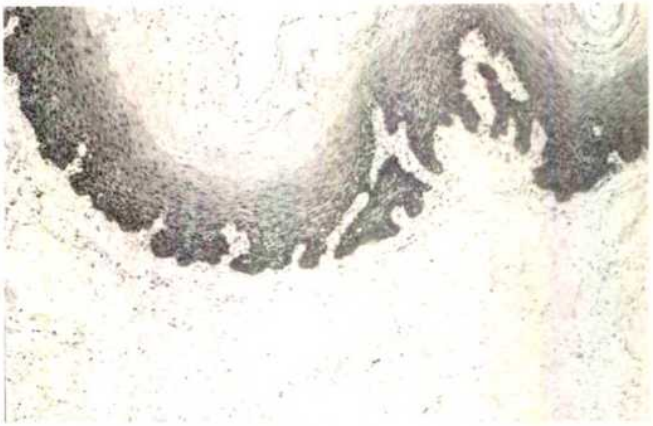

Figure 2 *Histological section of the area replaced by the collagen-coated Vicryl prosthesis. Collagen tissue has replaced the Vicryl mesh with complete epithelialization of the area*

In group A, one piglet showed evidence of moderate stenosis whereas the narrowing in the four remaining piglets was graded as minimal. In group B, five piglets showed minimal stenosis while one suffered severe stenosis. The piglet with the severe stenosis increased its weight by a factor of only 1·25 over the 4 weeks, compared with an average value of 3·17 times the original weight for the remainder of the animals in this group. In group C, the two surviving piglets showed moderate and severe stenosis respectively. Macroscopic examination of the piglets in group A revealed no sign of the prosthetic material that had been used to seal the gap 1 month previously. Histological findings of group A piglets revealed complete epithelialization of the area which had been replaced by the collagen-coated Vicryl prosthesis. It also confirmed that there was no evidence of residual Vicryl mesh, the prosthetic material having been completely replaced by new host collagen (*Figure 2*). Group B piglets revealed only a small scar with occasional granulation tissue where a suture still remained. In all four group C piglets that died, there was evidence of acute inflammation with disruption of sutures at the anastomotic site; the two surviving piglets had signs of chronic inflammation with superficial abscesses.

Discussion

The results presented in this study have shown that after repair of a full thickness defect in the oesophagus of growing piglets with a patch of collagen-coated Vicryl mesh, the prosthetic material degrades without trace and can be replaced by new host collagen with a normal epithelial lining. Furthermore, under the conditions of our experiments, the healing process was accompanied by minimal stenosis at the repair site with a normal epithelium. Of the six animals that had the collagen-coated Vicryl prosthesis, one animal died as the result of a leak from the anastomotic site. It should be emphasized that this was the first piglet on which such an operation was attempted. The remaining five piglets in this group grew as well as those in control group B in which no tension was applied to the resected oesophagus. However, the piglet with the more severe stenosis showed the least weight gain over the 4-week period.

The fact that an anastomosis performed under tension is clearly a source of problems was demonstrated by the difference in the two control groups. In group C, where a 2·5-cm length of oesophagus was removed before the anastomosis, only two animals survived the 4-week period and, even then, clear evidence of mediastinitis could be demonstrated in these animals at post mortem. In addition, moderate and severe stenosis at the site of the anastomoses could be seen in these two piglets both by visual inspection and by X-ray examination. In contrast to group C, however, five of six animals in group A survived following anastomosis in which no tension was applied to the anastomosis site by removing a section of oesophagus. These showed only minimal stenosis. Furthermore, unlike all the group C animals in which clear evidence of mediastinitis could be demonstrated histologically, together with disruption of sutures and inflammation at the anastomotic site, group A animals showed little evidence of ulceration.

Collagen-coated Vicryl mesh has already been applied to the protection of oesophageal anastomoses in 27 adult patients[9] with encouraging results, including a decrease in the rate of postoperative fistula formation at the operative site. It should be emphasized, however, that the material was wrapped around the anastomotic site and was not tested in 'growing patients' as would pertain in oesohageal atresia; nor was an attempt made to replace a full thickness tissue defect. Another study attempted the replacement of 4 cm of cervical oesophagus with a tube of Vicryl mesh[10]. However, severe problems were encountered with stenosis, and dehiscence at the operative site was a considerable problem, presumably because Vicryl mesh is not leakproof unless given a collagen coating.

Our own results have demonstrated that the collagen-coated Vicryl mesh degrades without trace at 4 weeks and can be used in the repair of full thickness defects where it is replaced by host scar tissue with a normal epithelium. The results are sufficiently encouraging to indicate that such material may be useful in the reconstruction of a section of oesophagus or as a means of reducing anastomotic tension, a factor clearly contributing to operative failure at oesophageal anastomoses.

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Yersinia infections in surgical practice

S. E. A. Attwood,
M. T. Cafferkey and
F. B. V. Keane

Department of Clinical Surgery,
Meath and Adelaide Hospitals, and
Department of Clinical
Microbiology, Trinity College at
St James' Hospital, Dublin, Ireland
Correspondence to:
Mr F. B V Keane, Meath
Hospital, Heytesbury Street,
Dublin 8, Ireland

This article reviews the clinical manifestations of Yersinia *bacteria emphasizing their recent rise in incidence and describing how* Yersinia *infection presents to the general surgeon. Geographical variations, patterns of disease, pathogenicity and the problems in diagnosis and management are discussed. This common but often unrecognized infection is usually self-limiting but the very young, the very old and the immunocompromised are at greater risk and prompt treatment is required to save lives.*

Keywords: *Yersinia enterocolitica, Y pseudotuberculosis,* gastroenteritis, abdominal pain, appendicitis, arthritis

Although first described by Schleifstein and Coleman in 1939[1] infection with bacteria from the *Yersinia* group was rarely diagnosed before the 1960s. At that stage most diagnoses were made in patients with self-limiting colitis or mesenteric adenitis[2,3] Since then it has become apparent that *Yersinia* species produce a variety of diseases with severity ranging from self-limiting to life-threatening, especially in the very young, the very old or the immunocompromised. Since 1970, when the genus was formally united[4], the number of cases diagnosed has risen exponentially[5,6]. Whether this increase reflects an increased awareness of the organism, a rise in the true incidence of disease or an improved diagnostic capability is uncertain.

By far the majority of illnesses are gastrointestinal in nature, usually with associated abdominal pain or diarrhoea, hence the frequency with which they present (often unrecognized) to the general surgeon. As well as this, yersiniae are capable of producing suppurative infections in many organs, various inflammatory reactions such as arthritis and thyroiditis, and occasionally overwhelming infections such as septicaemia and meningitis.

Characteristics of Yersinia bacteria

Yersinia species include *Y. pestis* (*Pasteurella pestis*), *Y. pseudotuberculosis* (*P. pseudotuberculosis*), *Y. enterocolitica* (*Pasteurella X*), *Y. frederiksenii, Y intermedia* and *Y. kristensenii* and are all members of the family *Enterobacteriaceae*[7]. The pathogenic serotypes of *Y. enterocolitica* include 0 3 (worldwide), 0:5, 0:6, 0:7, 0:8 (North America), and 0.9 (Europe)[5]. *Y. pseudotuberculosis* has at least six pathogenic serotypes (I–VI) but the relative pathogenicity of each type has not been fully investigated[8]. *Y. pestis* is the cause of bubonic plague and the remaining *Yersinia* species (*Y. frederiksenii, Y intermedia* and *Y. kristensenii*) have only been described in occasional reports

Yersiniae are Gram-negative rods, and their biochemical profiles are included in the commercial multitest systems and in the computerized identification schema that are used in most laboratories. The bacteria grow on a variety of culture media but colonies are small and slow growing compared with other enterobacteria. They are characteristically pale lactose non-fermenters whereas colonies of *Escherichia coli* are pink lactose fermenters. *Yersinia* species have a preference for cold environments. Their optimal culture temperature is 22°C[9] and it is at this temperature that they are motile[10], they are non-motile at 37°C They can continue to grow at or below 4°C. As there may be a natural reservoir of organisms in meat, particularly pork[11,12] and vegetable products[13], the normal processing and refrigeration of these foodstuffs may allow continued growth of these organisms[14]. Their ability to grow in the cold may also explain the significant seasonal variation of clinical infections which are maximal in the cooler months of the autumn and winter[15–17].

Most infections are sporadic or endemic. There have been a few well-documented epidemics of yersiniosis from village drinking water[18,19], from infected milk[20] and from milk chocolate[21]. The mode of spread in the majority of cases is oral ingestion of contaminated food[22]. Although *Y. enterocolitica* has been found to infect a wide variety of animals, notably chinchillas, hares, sheep, horses and cattle, most of the reported infections in these animals have been with serotypes that are not found in the human disease However, pigs (and less frequently cats and dogs) have been regarded as the main reservoir for human infections[23]. In the case of *Y. pseudotuberculosis*, zoonosis has also been reported[24]. For both species occasional outbreaks of familial[25–27], hospital[28,29], transplacental[30] and blood transfusion[31] infections have occurred.

Geographical variations

The geographical variation in *Yersinia* infections is of particular interest Yersiniosis has been reported from most parts of the world but there is a marked variation in both the frequency and the serotype pattern of the disease in different countries Although first described in Britain in 1960, relatively few cases are diagnosed in Britain and Ireland today However, the incidence is rising rapidly[6] The northern European countries of Belgium, the Netherlands and Scandinavia have recognized *Y. enterocolitica* as an important bacterial cause of gastroenteritis for many years[32,33] but, despite its frequency in these northern European countries, it is a relatively rare disease in neighbouring France.

The USA[34], Canada[35], Japan[36] and Australia[37,38] have all reported large numbers of cases in geographical pockets and the range of pathogenic serotypes differs from the European experience. Infection with *Yersinia* species has been regularly reported from eastern Europe and Russia, usually from contamination by yersiniae of foodstuffs and drinking water[39]. The cause of such marked variation in geographical pockets is something of an enigma. It is not due to an inability to grow

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the organism, or to a lack of surveys to search for it. Socioeconomic factors, dietary customs, farming and food storage methods have been implicated but, currently, there is no satisfactory explanation to account for the geographical variations of *Yersinia* infections.

Patterns of disease

Gastrointestinal

When specifically sought using selective techniques, *Y. enterocolitica* is a common isolate from stool cultures of patients with gastroenteritis. In northern Europe *Y. enterocolitica* is ranked immediately below *Salmonella* in frequency of isolation from cases of gastroenteritis and is of the same order of frequency as *Shigella*, *Campylobacter* and *E coli*[5]. *Yersinia* gastroenteritis is usually acute in onset, mild to moderate in severity and associated with malaise, pyrexia, abdominal pain and erythema nodosum[32]. Other extraintestinal symptoms may also present during the acute attack. The condition lasts from a few days to a few weeks but in most cases is self-limiting and resolves without treatment[40], although excretion of the organisms in the stool may continue for several weeks Enteritis with *Y. enterocolitica* may however progress to early fulmination, with toxic dilatation[41] and perforation of the ileum[42] or colon[43], and these cases will require immediate surgical intervention. Unfortunately there is no way of predicting such progression and diagnosis rests on clinical observation.

Yersinia is a common cause of acute terminal ileitis[44–46], diagnosed at laparotomy, and this is particularly associated with *Y. enterocolitica*. Despite occasional reports[47], no definite relationship has been identified between *Yersinia* and either Crohn's disease[48,49] or ulcerative colitis, but there are many cases of chronic non-specific inflammatory bowel disease that may be the end result of enterocolitis due to *Y enterocolitica*[50,51].

The predilection of *Yersinia* infections to the right iliac fossa is not confined to the terminal ileum. Both *Y. pseudotuberculosis* and *Y. enterocolitica* are frequent causes of mesenteric adenitis[2,52,53]. *Y enterocolitica* 0·9[33] and *Y pseudotuberculosis* appear to cause more abdominal pain syndromes than bowel disturbances and these include a spectrum of right iliac fossa pains that range from the non-specific to mesenteric adenitis (predominantly *Y. pseudotuberculosis* serotype I), acute terminal ileitis and actual appendicitis (predominantly *Y. pseudotuberculosis* serotype IV)[54].

The association of *Yersinia* infection with appendicitis was first suggested by Winblad *et al* in 1966[55], when they demonstrated a 6 per cent prevalence of antibodies to *Y enterocolitica*. At that stage the only serotype of *Y. pseudotuberculosis* that was considered pathogenic was serotype I and few workers considered it in their investigations Since then, Jepsen *et al.*[56] and others [57–66] have cultured *Y. enterocolitica* from appendices and have demonstrated rises in related specific antibodies. In one recent study *Yersinia* infection was present in 31 per cent of acute appendicitis cases (27 per cent *Y. pseudotuberculosis* and 4 per cent *Y. enterocolitica*) and the predominant serotype was *Y. pseudotuberculosis* IV[54].

The relationship of *Yersinia* to acute appendicitis deserves further study. It may be that suppurative appendicitis is a secondary infection of an appendix that is primarily infected with *Yersinia* and that those cases that are labelled right iliac fossa syndrome or non-specific abdominal pain have *Yersinia* infection in the lymphoid tissue of the appendix, terminal ileum or mesenteric nodes, or a combination of these, with spontaneous resolution. This hypothesis provides a useful working guide to the pattern of *Yersinia* infections in acute abdominal pain syndromes. In the majority of cases the clinical outcome of *Yersinia* appendicitis, mesenteric adenitis or acute terminal ileitis is no different from any of these conditions without proven yersiniosis[54,66] However, chronic colitis and abdominal pain after appendicectomy have been reported[41,54] and these sequelae are easily treated with appropriate antibiotics.

Other gastrointestinal infections have been reported less frequently Small bowel gangrene[67], intussusception[68,69], primary peritonitis[70–72], hepatic abscesses[73–75] and pancreatitis[76] have been occasionally reported and these more serious conditions are often found in debilitated or immunocompromised patients

Children

Yersinia as a cause of non-specific abdominal pain and diarrhoea in children has received considerable attention[21,77–85] The pattern of disease is age dependent and by far the commonest serotype identified has been *Y. enterocolitica* 0:3 (*Table 1*) In children under the age of 5 years an acute self-limiting diarrhoeal illness occurs, while in those over the age of 5 years apparent pseudoappendicitis predominates[61]. In children with non-specific abdominal pains or enteritis there is often an associated pharyngitis, and throat swabs from such children have demonstrated *Y. enterocolitica* as the sole infecting organism[21] *Yersinia* has also been cultured from uncomplicated cases of pharyngitis[86].

Suppurative infections

Yersinia as a cause of acute suppuration is relatively rare. Cultures from pus from pyomyositis[87], lung abscesses[88,89], occasional pneumoniae[90], cerebellar abscesses[5], lymphadenitis[32] and osteomyelitis[91,92] have yielded growths of *Yersinia* species, both *Y. enterocolitica* and *Y. pseudotuberculosis.*

Generalized fulminating infections

Many cases of *Yersinia* septicaemia have been reported and 50 per cent of these were fatal[24,63,79,92–95]. In general, *Yersinia* septicaemia has been reported in the already debilitated, or in those with thalassaemia major, haemochromatosis, or other form of iron overload[96], usually receiving treatment with desferrioxamine

Immunologically mediated disease

Yersinia infections have been related to the development of a number of non-suppurative inflammatory conditions The most frequent of these is acute arthritis, and in Scandinavia *Yersinia* is regarded as the commonest cause of acute non-rheumatoid joint inflammation[97–100]. The arthritis is mono- or polyarticular, commences after a latent period of 1–3 weeks and produces joint swellings which on aspiration show the presence of a moderate lymphocytosis Extension to other arthritic syndromes includes ankylosing spondylitis and Reiter's syndrome, and those with the histocompatibility antigens HLA B27 are known to be more susceptible[101]. Erythema nodosum[32,98] and tenosynovitis[32] are frequently found in *Yersinia* infections, either on their own or in combination with an antecedent history of acute gastroenteritis and fever or with a concomitant acute arthritis.

An association of thyroid inflammatory disorders[102] and *Yersinia* antibodies has been demonstrated but in some cases this has been correlated with the production of thyroid autoantibodies[103] and the relationship may be due to the presence of *Yersinia* infection at some remote site, precipitating the development of autoantibodies owing to a shared antigenic

Table 1 *Frequency of bacterial isolation from children with gastroenteritis in major European and North American centres*

	Sweden (Uhnoo *et al.*[84])	Canada (Marks *et al* [82])
Yersinia enterocolitica	5·6	2·8
Escherichia coli	4·2	—
Campylobacter	2·8	—
Salmonella	2·8	4·4
Shigella	0·7	1·1

The values are percentages

structure. Whether such a relationship pertains to the development of a *Yersinia* IgA glomerulonephritis[104–106] or whether this rare condition is due to the deposition of *Yersinia*–antibody complexes in the renal basement membrane is not yet known[107]. A similar association has been made between *Yersinia* infection and myocarditis and pericarditis[32].

Diagnosis

The diagnosis of *Yersinia* infection rests, ideally, on the combined culture of the organism and demonstration of a rise and fall of specific serum antibodies correlated with the clinical course of the disease[108]. In many cases the diagnosis cannot be made by culture owing to the inaccessibility of an infected site. Even in cases of gastrointestinal disease, where faeces provide an available culture substrate, the presence of *Yersinia* is not always correlated with specific disease.

The presence of *Yersinia* species in the stool could be due to the passage of transient non-pathogenic bacteria while the absence of *Yersinia* from the faeces does not exclude the presence of infection in the mesenteric nodes, or another site, from which no excretion of the organisms is occurring. Isolation of *Yersinia* species from the mixed growth obtained from faecal culture is limited by the small size and lack of distinguishing features of the colonies unless specific selective media or other techniques are employed By using prolonged cold enrichment and a bench microscope the pick-up rate can be greatly increased[109]. Thus in many cases the diagnosis rests on the demonstration of a rise of specific antibody to a single pathogenic *Yersinia* serotype[108].

The need for serial sampling has recently been stressed and this introduces a delay of 10 days or more in the diagnostic process[54]. The problem of detection is made more difficult by the need to test serum against every known *Yersinia* pathogen, amounting to more than ten serotypes in many areas.

A variety of methods for antibody detection have been described. One of the most accurate is enzyme-linked immunosorbent assay[110], but direct tube agglutination (with adequate dilutions to avoid the prozone phenomenon)[108] and the differential detection of IgA and IgM antibodies by specific techniques are practical alternatives[111]. The specificity of these investigations is extremely high with a few notable exceptions. Antibodies to *Y enterocolitica* 0.9 cross-react with *Brucella* species[112] and this problem is difficult to resolve. Unless there is an endemic incidence of brucellosis, however, the problem is rarely of practical importance. Cross-reactivity of *Y. pseudotuberculosis* II with *Salmonella* of group B and *Y. pseudotuberculosis* IV with *Salmonella* of group D, however, is overcome by absorbing the serum with the cross-reacting antigens before measuring the agglutinating titre[34,54]

A fourfold rise in antibody titre or a significantly elevated titre with subsequent fall is compatible with the presence of invasive infection. In our own laboratory we recognize an antibody titre of 1/160 for *Y. enterocolitica* and 1/320 for *Y. pseudotuberculosis* as significantly elevated on direct tube agglutination, values similar to those used at the *Yersinia* reference laboratory in Leicester, UK[113]. The rise in serum antibody occurs after the first week of illness and remains elevated for a period of 1–3 months, depending on the course of the disease, before declining to normal levels[2,53,55,114].

Transient elevations of *Yersinia* antibodies occur in less than 2 per cent of the normal healthy population and, depending on the frequency of endemic infection, low titres may be present in normal subjects[54]. Cultures from appendices, mesenteric nodes and other resected material have yielded *Yersinia* species but the yield is low relative to the frequency of serum antibody rise[56]

Pathogenicity

The pathogenicity of *Yersinia* species is very variable and this creates difficulty in correlating the presence of these organisms with actual disease. A most significant finding was that of plasmid-mediated tissue invasiveness discovered by Zink *et al.* in 1980[115]. *Y. enterocolitica* was the first bacterium in which this plasmid effect was demonstrated and this phenomenon has since been shown in *Salmonella*, *Shigella* and *E coli*. The plasmid causes a number of changes in surface proteins and induces resistance to the bactericidal effect of human serum[116,117] and to the immune mechanisms of the intestine in rat models[118].

Animal models show that the initial events in the pathogenesis of *Y. enterocolitica* infection are entry of the organisms into cells, followed by intracytoplasmic replication[119]. It is not yet known whether the production of enterotoxin by yersiniae is relevant to the development of enteric disease but it has been shown that *Y. enterocolitica* will produce toxins only when the bacteria are grown in cell lines and not on nutrient media[120]. Thus if *Yersinia* toxin does play a role in enteritis it must either be ingested or be produced only after invasive infection rather than during intraluminal replication.

Another major factor in the pathogenicity of *Yersinia* species is their predilection for iron[121]. Unlike most other aerobic bacteria, yersiniae produce no detectable iron-binding compounds, or siderophores, and must utilize iron bound by other bacteria. Hence it can flourish in the intestine but in the tissues it must compete with host iron-binding proteins for available iron. Whether this explains its predominance in the area of the terminal ileum where iron is absorbed is purely conjectural. However, in patients with conditions such as iron overload, thalassaemia[122] and haemochromatosis, particularly when treated with desferrioxamine[24], the organism has a ready supply of iron and can thrive (desferrioxamine is a bacterial iron-binding protein or siderophore). Even patients with accidental iron overdose who have been treated with desferrioxamine have died from *Y. enterocolitica* septicaemia[123].

Alcoholism, cirrhotic liver disease and diabetes mellitus all increase the susceptibility to and severity of *Yersinia* infections[124,125].

Pathological features

Macroscopically, *Yersinia* produces few distinguishing features. In the gastrointestinal tract, inflammation produces diffusely swollen, erythematous and friable mucosa[46,51]. The inflamed mucosa of the colon may be covered by a pseudomembrane and the serosal surfaces may be covered by a serosanguinous, fibrinous exudate so that loops of bowel become focally adherent. Ulcers occur and are small, shallow and oval, similar in appearance to aphthoid ulcerations seen in Crohn's disease[43,48,126,127]. Microscopic examination shows chronic non-specific inflammation with infiltration of mostly mononuclear cells and lymphocytes and few polymorphonuclear cells[128] Plasma cells, giant cells or sarcoid-like granulomas are rarely found in colonic disease but sections of infected mesenteric nodes and lymphoid tissue in appendices and the Peyer's patches of terminal ileum have shown granulomas, microabscesses and necrosis of the lymphoid follicles[128,129].

The degree of local tissue destruction in these infections is very variable. Correlation from animal experimental work is difficult as strains that are pathogenic to humans have variable pathogenicity in mice, gerbils, guinea pigs and rabbits[130–134].

Strains of *Y. pseudotuberculosis* that cause mild illness in humans have produced an overwhelming mesenteric adenitis in monkeys that proves rapidly fatal[135–137]

Management

Knowledge of the presence of *Yersinia* infection influences the management of the patient in a number of ways. In the majority of intestinal conditions, no specific treatment is required other than general supportive measures. Most cases of abdominal pain or diarrhoea are self-limiting and the diagnosis is often made retrospectively. Prolonged illness is an indication for specific therapy. Early treatment of yersinial arthritis is recommended as spontaneous resolution may take several weeks. Whether antibiotic therapy prevents the development of ankylosing spondylitis or related complications is uncertain Patients with acute or chronic colitis or chronic abdominal pain show rapid improvement with relevant antibiotic therapy[54].

Suppurative forms should be treated by traditional surgical drainage and institution of antibiotics *Yersinia* species are sensitive to tetracyclines, aminoglycosides, co-trimoxazole and chloramphenicol[34]. Most are resistant to penicillins and cephalosporins as yersiniae produce a number of β-lactamases[138]. *In vitro* sensitivity to nitrofurantoin is often demonstrable but nitrofurantoin lacks *in vivo* activity. The usual antibiotics of choice are tetracycline, co-trimoxazole and chloramphenicol, depending on the severity of the illness and the age of the patient.

In cases of right iliac fossa pain the use of antibiotics cannot replace the need for surgery of suspected appendicitis. Even if a rapid serological diagnosis could be made it would not obviate the potential progression to suppurative appendicitis and treatment must be guided by the clinical signs. However, in patients with protracted non-specific abdominal pain a serological diagnosis of *Yersinia* infection indicates the need for antibiotic therapy which is usually effective[54] In most patients with *Yersinia*-related appendicitis no change in therapeutic policy is required. The exceptions are those rare cases of patients with persistent postoperative right iliac fossa pain where tetracycline has proved useful[32].

Antibiotic treatment of the inflammatory disorders of thyroiditis and glomerulonephritis is unlikely to be helpful but Reiter's syndrome, erythema nodosum and tenosynovitis have improved with tetracycline therapy.

Identifying *Yersinia* species as the causative organism of disease in the community or hospital environment raises questions about the source of infection. *Yersinia* infections in hospital patients with diarrhoea or an open infected wound are a potential source of nosocomial infection Despite the fact that many foodstuffs and drinking sources have been identified as a source of infection, the origin of most cases of yersiniosis remains obscure Further work in this direction might not only identify the source but could provide the means to reducing the incidence of such common illnesses as appendicitis, gastroenteritis and acute arthritis

Conclusions

Acute infections, ranging from self-limiting gastroenteritis to severe gangrenous colitis with perforation and/or septicaemia, are associated with infection by *Y. enterocolitica* and *Y. pseudotuberculosis* It is now clear that the infection is zoonotic and human isolates are usually pathogenic. *Y. enterocolitica*, which is now the most common *Yersinia* type isolated, shows a marked geographical variation While *Y enterocolitica* 0 3 is found worldwide, 0 9 is prevalent in northern Europe, and 0:8 in North America In addition, it is clear that many human and environmental isolates are of low pathogenicity while some serotypes are highly virulent

In surgical practice, *Yersinia* infections are usually associated with the gastrointestinal tract *Y. pseudotuberculosis* is the most frequent bacterial cause of acute mesenteric lymphadenitis and is associated with acute terminal ileitis or acute appendicitis. In contrast, invasive and non-invasive enterotoxin producing strains of *Y enterocolitica* are a frequent cause of self-limiting gastroenteritis Invasive strains are the most common recognized bacterial cause of acute terminal ileitis. They also cause non-specific abdominal pain or 'pseudoappendicitis' and, occasionally, acute colitis or acute appendicitis. *Y. enterocolitica* 0.8 which has been isolated only in the North American continent causes a severe gangrenous enterocolitis which may be fatal. Except in rare circumstances, surgeons will not encounter this infection causing clinical problems for two reasons. The first is the variability in clinical presentation and geographical variation in incidence and prevalence of the different *Yersinia* serotypes. The second and more important reason is that *Yersinia* infections are usually self-limiting and in only a minority of cases does the infection become life-threatening. Microbiological reference laboratories provide specialized investigations to assist in the diagnosis of difficult cases but discretion should be exercised in their use. However, surgeons should be aware of the epidemiology and spectrum of organisms that infect their environment so that they may be able to recognize those patients that require accurate diagnosis and specific therapy.

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Leucine kinetics in surgical patients I: a study of the effect of surgical 'stress'

R. A. Harrison, M. R. Lewin, D. Halliday* and the late C. G. Clark

*Department of Surgery, University College London and *Nutrition Research Group, MRC Clinical Research Centre, Watford Road, Harrow, UK*

Correspondence to:
Mr R A. Harrison, Department of Surgery, Edgware General Hospital, Edgware, Middlesex
HA8 0AD, UK

At present there is no consensus about the effect of surgical and accidental trauma on protein metabolism. Leucine kinetics, an index of protein turnover, have been studied in ten patients before intra-abdominal surgery and on either the third (n=5) *or seventh* (n=5) *postoperative day. Only small changes in leucine kinetics were noted in the early postoperative study but, by the seventh day, there was evidence of increased synthesis as part of an overall elevation of turnover rates. It is suggested that the previously expressed opinion that protein synthesis is reduced after surgery must be re-examined.*

Keywords: Leucine kinetics, protein turnover, surgery, surgical stress

Protein metabolism is a dynamic process. Although this concept was first suggested by Magendie in 1823[1], it was not established scientifically until the work of Schoenheimer was published posthumously 40 years ago[2]. In the last decade, isotope tracer methods which are able to quantify the dynamic aspects of protein turnover have been used to examine the nature of the disturbed nitrogen metabolism observed after surgical and accidental trauma. Such studies, it has been suggested[3], could form the basis of a greater understanding of the pathophysiology of nitrogen loss and therefore contribute to the development of more rational methods to modify the nitrogen loss in traumatized patients. Furthermore, these methods might also be used to monitor the effects of such therapy biochemically.

Since isotope tracer studies were introduced to this area of surgical research there have been several independent studies. Opinion is equally divided between those authors who report increased protein synthesis after trauma[4–7], and those who observed suppression of activity[8–11]. One report[12] failed to show any change. Several authors have commented on this dichotomy and are agreed that nutritional factors probably account for much of the apparent disparity[6,12]. Furthermore, these data have been obtained using six distinctly different methodologies and variable timing of the postoperative study.

In an attempt to clarify these apparently contradictory results, a study using a well-established isotope tracer method has been carried out in ten patients before and after intra-abdominal surgery.

Patients and methods

Patients, before resectional surgery for colonic neoplasms, were randomly allocated to one of two groups. Patients in group 1 ($n=5$) had an infusion study preoperatively and a second 7 days after surgery. Patients in group 2 ($n=5$) also had a preoperative measurement but the postoperative infusion study was carried out 3 days after surgery. Anthropometric details of the two study groups and the operative procedure carried out are given in *Table 1*. Lean body mass (LBM) was calculated from the patient's height and weight[13]. Postoperatively no patients received any nitrogen intake and fluid balance was maintained with normal saline and 5 per cent dextrose (1675 kJ day^{-1}). Leucine kinetics were measured after a 12-h fast using a primed, constant infusion of L-[1-^{13}C]leucine[14]. The [^{13}C]leucine enrichment was 99 per cent (KOR Isotopes, Cambridge, Massachusetts, USA). At the start of each infusion a bolus injection of L-[1-^{13}C]leucine (1 mg kg^{-1}) and labelled bicarbonate (0·16 mg kg^{-1}) was given to prime the relevant pools. An infusion of L-[1-^{13}C]leucine (1 mg kg^{-1} h^{-1}) was continued throughout the study, which lasted for 6 h. Samples of plasma and expired air were collected every 30 min once a plateau was established. Two measurements of carbon dioxide production rate were made using a timed Douglas bag collection method. The ^{13}C-enrichment in plasma α-ketoisocaproate was measured using a gas chromatograph mass spectrometer, using the derivatization procedure of Rocchiccioli *et al*[15]. α-Ketoisocaproate measurements were made rather than leucine as it has been suggested that they reflect more accurately the enrichment close to the site of protein synthesis[16]. The ^{13}C-enrichment in expired air was measured using an isotope ratio mass spectrometer. This was used to calculate the four parameters of leucine turnover (flux, leucine oxidation, leucine release 'from' and incorporation 'into' protein) using the formulae proposed by Matthews *et al*[17]. These are based on a simple model of protein metabolism that contains a single pool of protein in equilibrium with a second single pool of amino acids (*Figure 1*). In a steady state it is assumed that movements in and out of the amino acid pool, known as flux (Q), are equal. Amino acids enter the pool from dietary sources (I) and as a result of protein breakdown (B); they leave the pool when incorporated into protein (S) or when oxidized (C). Thus in a steady state.

$$Q=I+B=S+C$$

Results were expressed as micromoles of leucine per kilogram LBM per hour. This may be converted to grams of protein per kilogram per day using the conversion factor 590/24, but this conversion is valid only if it is accepted that leucine is a reliable tracer for whole body protein and that leucine represents 7·8 per cent of mixed body protein[17].

The results were expressed as medians and ranges and analysed by non-parametric statistics using the Mann-Whitney U test. Confidence intervals have been advocated for use in reporting results[18], and for groups of five analysed non-parametrically the range represents the 94 per cent confidence interval.

Results

The parameters of leucine turnover, flux (Q), synthesis (S) and breakdown (B) were well matched in the two groups preoperatively. Full details of the pre- and postoperative kinetic data are given in *Table 2* (group 1) and *Table 3* (group 2). It should be noted that oxidation of leucine (C) was in fact significantly higher in group 2 preoperatively ($P<0·05$). The reason for this was unclear. There was an increase in flux postoperatively when measured on the seventh day (group 1). A similar trend was evident in the early postoperative study (group 2); however, the confidence interval straddles zero. In a fasted patient, flux (Q) is equal to breakdown (B) as there is no contribution from exogenous sources of leucine. Considering the data that relate to synthesis (S), in group 1 there was a wide range but the results exclude a significant reduction in synthesis postoperatively. A similar result was obtained in group 2. However, the range is smaller and the results are grouped around zero, suggesting no clinically significant change in synthesis. The efficiency of nitrogen reutilization was measured by examination of oxidation as a percentage of flux (C/Q per cent). The higher the value of this index, the lower the efficiency. On first inspection the data suggest a more

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Table 1 *The physical characteristics of the patients in the two study groups and the operative procedure carried out*

	Age (years)	Weight (kg)	Lean body mass (kg)	Percentage of ideal weight	Operative procedure
Group 1					
Female	57	44·0	36·9	71	Left hemicolectomy
Male	72	78·1	62·5	110	Abdominoperineal resection
Female	64	46·3	37·7	80	Abdominoperineal resection
Female	68	53·1	39·9	105	Anterior resection
Female	71	57·0	40·7	109	Anterior resection
Group 2					
Female	74	63·5	41·9	130	Left hemicolectomy
Male	62	88·5	61·6	145	Left hemicolectomy
Female	62	56·8	42·7	107	Anterior resection
Female	72	70·3	47·4	130	Left hemicolectomy
Male	76	69·3	48·5	109	Anterior resection

Group 1, preoperative and 7 days postoperative measurement; group 2, preoperative and 3 days postoperative measurement

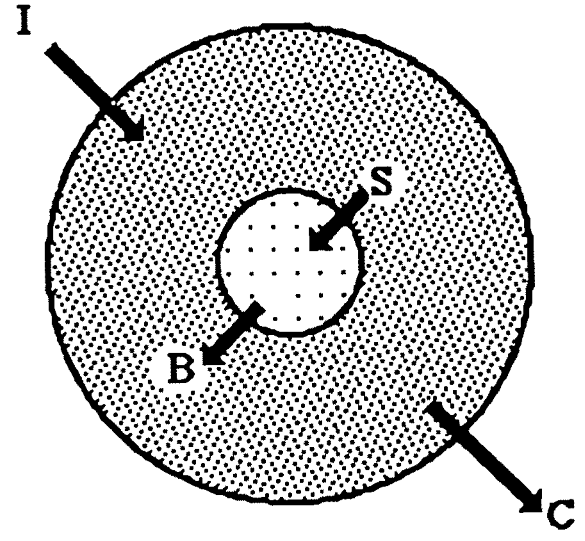

Figure 1 *The simplified model of protein metabolism used to calculate amino acid turnover.* B, *amino acids released from protein breakdown,* I, *amino acid intake;* S, *amino acids used for protein synthesis,* C,, *amino acid excretion* □, *Protein,* ▨, *amino acid pool.* Q=B+I=S+C (Q, *amino acid flux*)

Table 2 *Parameters of leucine turnover in group 1 showing the median and 94 per cent confidence intervals, preoperatively and 7 days postoperatively*

	Median (μmol kg^{-1} h^{-1})	Range and 94% CI (μmol kg^{-1} h^{-1})
Flux (Q) = breakdown (B)*		
Preoperative	137·8	102·5–216·3
Postoperative	160·8	142·6–215·7
Change in flux	30·7	−0·7–66·8
Oxidation (C)		
Preoperative	16·5	9·0–20·7
Postoperative	24·4	22·3–40·2
Change in oxidation	12·7	5·9–19·4
Synthesis (S)		
Preoperative	117·0	93·5–199·8
Postoperative	120·6	118·8–193·2
Change in synthesis	23·5	−6·5–54·0
C/Q(%)		
Preoperative	12·9	7·6–15·1
Postoperative	16·7	10·4–25·0
Change in C/Q	2·7	1·9–9·9

Results are expressed as micromoles of leucine per kilogram lean body mass per hour. CI, confidence interval (represented by range), * $Q = B$ in a fasted patient

marked deterioration in nitrogen economy 1 week after surgery (group 1) than was observed on the third postoperative day (group 2). However, it should be noted that there was an unexplained higher value for oxidation in the patients in group 2 before surgery and this was reflected in the preoperative value of oxidation as a percentage of flux. In group 2 the rate of nitrogen reutilization did not change but remained at the lower level observed in this group before surgery.

Discussion

Studies of whole body protein turnover cannot be used to address the question of the clinical significance of nitrogen loss, although they may describe, in terms of net synthesis and breakdown, the basis of negative nitrogen balance The studies are descriptive and if such methods are to be used as a basis for future investigations the ambiguity that currently exists in the literature must be examined and where possible explained. Two of the early studies are commonly quoted as evidence for postoperative suppression of protein synthesis The study reported by O'Keefe *et al*[9] looked at four patients with a mix of surgical pathologies before and after surgery; however, the patients were fed preoperatively and fasted after surgery. Attention has been drawn to this flaw in the experimental design[5,6,8] The effect of nutrient withdrawal has been investigated in several studies and opinion is unanimous that fasting causes a reduction in protein synthesis. The reductions reported are between 30 and 40 per cent in burns patients[19], preoperative patients[6] and in volunteers[20,21] Thus the 12 per cent fall in protein synthesis postoperatively reported by O'Keefe *et al.*[9] is less than would be predicted as a result of nutrient withdrawal alone. The second study was the subject of two publications[10,22] There is no evidence about how many individual patient studies were common to both reports; however, the conclusions regarding flux are the same. There was no change in this parameter postoperatively in either report The conclusions concerning synthesis were, however, different· the initial report[22] showed no change after surgery and the second[10] showed a reduction This change may be attributable to differences in the method of measuring mean nitrogen loss for the purpose of the calculation In another study[11] children were studied before and after reconstructive

Table 3. *Parameters of leucine turnover in group 2 showing the median and 94 per cent confidence intervals, preoperatively and 3 days postoperatively*

	Median (μmol kg^{-1} h^{-1})	Range and 94% CI (μmol kg^{-1} h^{-1})
Flux (Q) = breakdown (B)*		
Preoperative	159·3	124·3–161·7
Postoperative	150·4	120·9–192·0
Change in flux	17·1	−9·0–28·5
Oxidation (C)		
Preoperative	26·0	21·0–35·2
Postoperative	35·7	16·5–42·9
Change in oxidation	1·8	−8·9–13·3
Synthesis (S)		
Preoperative	124·2	103·4–135·6
Postoperative	127·6	104·4–151·6
Change in synthesis	3·8	0–24·2
C/Q(%)		
Preoperative	18·4	16·9–22·1
Postoperative	20·3	13·7–24·1
Change in C/Q	−0·02	−5·9–5·7

Results are expressed as micromoles of leucine per kilogram lean body mass per hour. CI, confidence interval (represented by range), * $Q = B$ in a fasted patient

surgery The postoperative nitrogen intake was 22 per cent lower than the preoperative value and though statistical analysis shows this to be 'not significant' that does not ensure that there was no effect on the level of protein synthesis.

Nutritional intake was controlled by the administration of total parenteral nutrition in a later study[12] which reported that the parameters of protein turnover were not altered by surgery. Even this protocol was not ideal as there was a break in the administration of total parenteral nutrition over the surgical period and it was only restarted 2 h before the second study.

Two studies have been carried out after accidental trauma: one in burns patients[4] and the other following major skeletal injury[5]. In both studies an increase in protein synthesis was noted along with a rise in breakdown leading to a net nitrogen loss. Of three investigations carried out in the perioperative period, two[6,7] reported a general increase in turnover, including synthesis, in fed patients. In the other study[8] examining the effect of a synthetic growth hormone, a reduction in synthesis was noted as part of an overall reduction in turnover in the control group. This study used a 24-h primed constant infusion of [^{15}N]glycine and subjects were fasted only for a period of 6 h before the start of the infusion. There is evidence to suggest that patients do not achieve a basal state in such circumstances and that the data obtained using a ^{15}N-methodology will reflect the previous fed state[21]. When dietary intake was fully controlled by intravenous feeding and turnover was measured using a very similar primed constant infusion methodology, turnover (including synthesis) was increased postoperatively[7].

From this review it is possible to conclude that several reports suggesting a reduction in synthesis postoperatively can no longer be accepted in support of that hypothesis without significant reservations. The evidence is that unless there is absolute comparability of nutritional intake, the effects of surgery may be masked by greater changes resulting from nutritional factors.

The present study has approached this problem by carrying out both pre- and postoperative studies in the fasted state; even this protocol is a compromise and does not give absolute comparability The preoperative study followed an overnight fast, while the postoperative measurements were made after a further 3 or 7 days during which there was no nitrogen intake and only 1675 kJ day^{-1} of energy supplied. The data available suggest that this is an acceptable protocol Using a leucine-based method it has been demonstrated that synthesis falls by 40 per cent within 12 h of starting a fast, and after 3 weeks on a low calorie, no nitrogen regimen subjects still had a synthesis rate 40 per cent lower than normal[23]. The results from the present study support the hypothesis that there is no reduction in synthesis after surgery. Indeed there is a suggestion that it may rise as part of an overall increase in turnover

This observation is very much in keeping with the traditional view of the metabolic response to stress. When the negative effects of nutrient withdrawal on protein synthesis are excluded then the predominant effect of stress would appear to be anabolic. This response is characterized by the production of the acute phase proteins, immunoglobulins and the proteins required for tissue repair. Many of these proteins have very short half-lives and the increased plasma levels are associated with high rates of protein turnover. In the absence of an external source of nitrogen, as nitrogen turnover is less than 100 per cent efficient, this increase in protein synthesis must be matched by an even greater level of nitrogen release. These changes result in the observed negative nitrogen balance. It can be argued that such an increase in turnover, despite its adverse effect on the nitrogen economy, is advantageous to the organism as it ensures that there can be a rapid response to the variable demands for protein synthesis that characterize the period after injury.

The present study for the first time examined the question of time-related changes in protein kinetics after surgery. The results suggest that there is a lesser effect in the early postoperative period, when flux and synthesis remain close to preoperative values. By 1 week after surgery the results, while showing a wide range, suggest that the overall effect is one of increased turnover with both synthesis and breakdown increased. If it is accepted that the two postoperative studies were carried out under comparable nutritional conditions it is possible to speculate about other factors that might account for the biphasic postoperative response One possibility is the level of mobility, low in the early postoperative period and returning towards normal at 1 week. Immobility is a potent suppressor of protein synthesis[24], although no studies of bed rest and rehabilitation have been reported. The results of the present study suggest that time after surgery as well as nutritional intake should be standardized in any future studies.

It may be concluded both from the study reported here and from the literature review that in the case of accidental trauma the data suggest that protein turnover, including synthesis, is increased A similar pattern is suggested by some of the perioperative reports, including the present study. In each case where it is reported that synthesis is reduced postoperatively, there would appear to be an unacceptable level of nutritional control in the experimental design considering the known characteristics of the tracer methodology.

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Appendix

Some preliminary isotope data from this study were included in a previous publication[25]. Six patients, who received amino acid supplements postoperatively, have been excluded and one new patient added for this presentation. These changes were to ensure the pathological and nutritional comparability of the two groups.

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Leucine kinetics in surgical patients II: a study of the effect of malignant disease and tumour burden

R. A. Harrison, M. R. Lewin, D. Halliday* and the late C. G. Clark

*Department of Surgery, University College London and *Nutrition Research Group, MRC Clinical Research Centre, Watford Road, Harrow, UK*

Correspondence to:
Mr R A. Harrison, Department of Surgery, Edgware General Hospital, Edgware, Middlesex HA8 0AD, UK

Isotope studies of protein turnover have given conflicting evidence about the effects of a malignant tumour on the protein metabolism of the host. Leucine kinetics have been studied, as an index of protein turnover, using a well established methodology. Twenty patients were studied, five with benign disease of the colon, ten with localized malignant tumours of the large bowel, and five in whom there was evidence of metastatic disease from a colonic primary. No effect was observed on the leucine turnover of the patients that might be attributable to the presence or size of the tumour burden. It is suggested that some of the previously conflicting results may be attributable to variability in the experimental design, the heterogeneous patient groups studied and the methods used to express the results obtained.

Keywords: Protein turnover, leucine kinetics, malignant disease, tumour burden

Recently, practicable methods of measuring the dynamic aspects of protein metabolism have become available using both radioisotopes and stable isotopes as metabolic tracers. These methods have been used to investigate the inter-relationship between a malignant neoplasm and the nitrogen metabolism of the host organism. The first such study in humans[1] reported an increase in protein turnover which was proportional to the estimated tumour burden in patients with colorectal neoplasms. Later studies showed similar results in patients with a heterogeneous mix of tumours[2–4], in children with leukaemia and lymphoma[5] and in adults with non-oat cell carcinoma of the lung[6]. These results are in contrast to those in cachectic patients with lung tumours[7] and germ cell tumours[8]. Neither of these studies showed any effect of the tumour on host protein metabolism. Similarly, a study of patients before and after resection of colonic tumours failed to show any effect of tumour resection on protein turnover[9].

In an attempt to clarify these conflicting results a study was carried out in which leucine kinetics were measured in 20 patients, divided into four equal groups according to the colorectal pathology. One group had benign disease, two groups had 'localized' malignant disease (Dukes' A and B) and one group had metastatic disease.

Patients and methods

Details of the four groups are given in *Table 1* In each case the diagnosis and Dukes' classification were based on both clinical and histological results Nutritional status was assessed on the basis of body weight compared with standard values for height[10] and, biochemically, by measurement of serum albumin. Lean body mass (LBM) was calculated from the patient's height and weight using a standard formula method[11]

Leucine kinetics were measured both preoperatively and after a 12-h fast using a primed, constant infusion of L-[1-^{13}C]leucine. This methodology and its theoretical basis has previously been described in detail[12]. The central assumption is that in a steady state, leucine flux (Q) is equal to the sum of leucine released from protein (B) and leucine intake (I), which is in turn equal to the sum of leucine utilized in protein synthesis (S) and leucine oxidation (C), thus·

$$Q=B+I=S+C$$

The data were analysed by non-parametric statistics using the Mann–Whitney U test. The 95 per cent confidence intervals which have been advocated for use in reporting results[13] cannot be given for groups of five analysed non-parametrically as the range represents the 94 per cent confidence intervals

Results

The results for the anthropometric data and serum albumin levels on the four study groups are detailed in *Table 2*. There were no differences between the four groups with respect to weight, LBM or body weight as a percentage of ideal. However, despite well-maintained body weights and percentage weight for height, the patients with metastatic disease (group 4) had significantly lower serum albumin levels ($P<0.05$) than patients

Table 1 *Age, sex, diagnosis and classification in the four study groups*

	Age (years)	Diagnosis	Classification
Group 1			
Male	63	Diverticular disease	Benign
Female	72	Colonic adenoma	Benign
Male	64	Diverticular disease	Benign
Female	67	Diverticular disease	Benign
Female	61	Colonic adenoma	Benign
Group 2			
Female	57	Ca rectum	Dukes' A
Male	58	Ca left colon	Dukes' A
Female	80	Ca. rectum	Dukes' A
Male	72	Ca. rectum	Dukes' A
Male	76	Ca left colon	Dukes' A
Group 3			
Male	62	Ca left colon	Dukes' B
Female	62	Ca. rectum	Dukes' B
Female	75	Ca left colon	Dukes' B
Female	71	Ca. left colon	Dukes' B
Female	81	Ca. left colon	Dukes' B
Group 4			
Female	74	Ca. left colon	Metastases
Female	49	Ca splenic flexure	Metastases
Female	74	Ca rectum	Metastases
Female	74	Ca rectum	Metastases
Female	68	Ca rectum	Metastases

Ca , carcinoma

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in any of the other groups (*Table 2*). Leucine flux, which in the fasted patient is equal to the release of the amino acid from protein, is shown in *Figure 1*. Although the lowest median value was in the group with benign disease (group 1) and the highest in the group with metastatic disease (group 4), these differences were not significant. Leucine utilization in protein synthesis (flux–oxidation) is shown in *Figure 2*, and once again there was no significant difference between the groups. Similar comparisons can be made for oxidation of leucine and for oxidation as a percentage of flux which gives a measurement of nitrogen reutilization. In each case there was no difference between the patients with benign as opposed to malignant disease or when comparisons were made within the groups with malignant disease.

Discussion

With the introduction of isotope tracer techniques and their use in clinical investigations of surgical patients there was an expectation that some of the controversies concerning nitrogen metabolism in the tumour-bearing patient might be resolved and that this would lead to a greater understanding of the pathogenesis of the cachectic syndrome commonly observed in advanced malignancy[1]. Such an understanding, it was suggested, was a prerequisite to developing therapeutic protocols to mitigate the metabolic effects of tumours[14]. In the nine published studies there is a dichotomy of opinion concerning the inter-relationship of tumour and host protein turnover.

As experience in general has increased with isotope studies of protein turnover it has become apparent that the data obtained are often predetermined by the conditions of the study and the experimental design. Furthermore, the interpretation of the experiment can be influenced by the method of expressing the results. One of the most potent influences on the measured values of protein turnover is nutritional status and the nutritional intake during the study. Nutrient withdrawal reduces protein synthesis by up to 40 per cent[15,16] while refeeding a malnourished patient will cause a marked stimulation[17]. The Newcastle study[1] concluded that protein turnover was increased in those patients with advanced tumours. However, considering the group as a whole, the lowest protein turnover rates were seen in the patients with metastatic disease. Only when the group was subdivided according to the presence or absence of 'anorexia' were differences apparent. Analysis of this study was further complicated by the use of a feeding regimen on the day of the isotope study that was standard for all patients; for the anorexic group this might have represented an increase on their prior intake. This study illustrates some of the problems in carrying out isotope studies of protein turnover in patients in whom the nutritional status and nutrient intake cannot be standardized. Objective measurements of intake can be made[18] and are preferable to the subjective assessment of anorexia. 'Refeeding' should be avoided as this will have an unpredictable, probably stimulating, effect on protein turnover.

Table 2 *Anthropometric data and serum albumin levels for the four study groups*

Study group	Weight (kg)	LBM (kg)	Body weight as percentage of ideal	Albumin (g l^{-1})
1 Benign	64 (54–70)	47 (45–47)	117 (80–130)	42 (35–43)
2 Dukes' A	69 (44–82)	49 (37–63)	109 (94–126)	41 (36–42)
3 Dukes' B	57 (42–89)	41 (36–62)	107 (87–145)	41 (39–42)
4 Metastases	58 (53–64)	41 (39–46)	109 (87–145)	36* (32–39)

Median values are given, with ranges in parentheses. LBM, Lean body mass; * $P<0.05$ compared with groups 1, 2 and 3

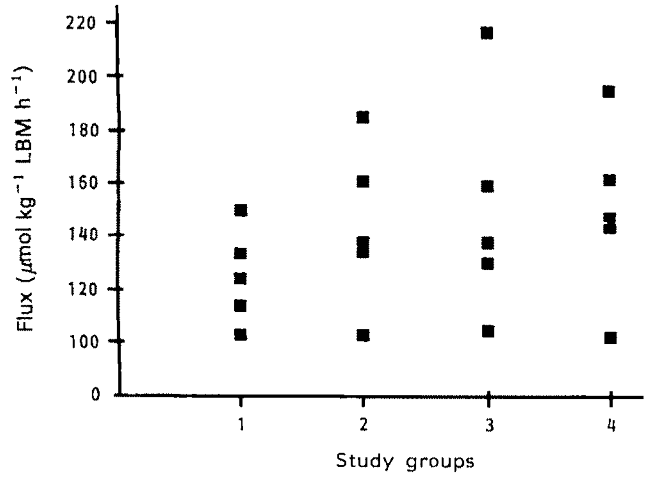

Figure 1 *Leucine flux* (Q) *which equals leucine release from protein* (B) *in the four study groups: group 1, benign; group 2, Dukes' A; group 3, Dukes' B; group 4, metastatic disease. LBM, Lean body mass*

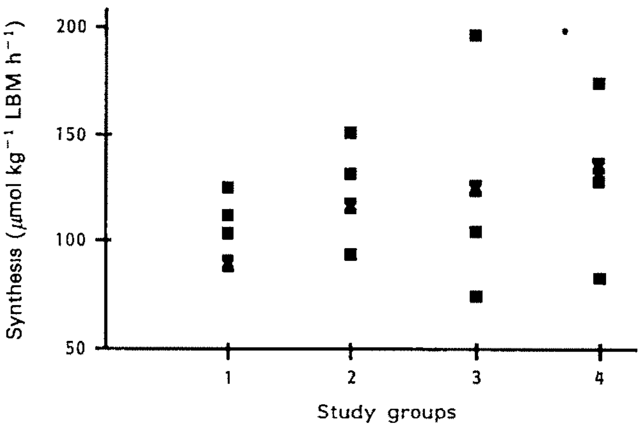

Figure 2 *Leucine incorporation into protein* (S) *in the four study groups: group 1, benign; group 2, Dukes' A; group 3, Dukes' B; group 4, metastatic disease. LBM, Lean body mass*

Many of the studies reported have examined both male and female patients. This, combined with the effects of variable weight loss and a wide age range, will result in a study population of widely differing body composition. While accurate measurement of total body nitrogen or potassium may not be possible, the practice of reporting results 'per patient'[8] is unacceptable unless two studies on the same patient are compared[9]. Even reporting results 'per unit whole body weight'[1–7] might introduce a bias towards higher figures for turnover in patients with low body fat stores and in children[5]. The use of some expression of metabolic mass or lean body weight is recommended to reduce these errors, and in the present study results were expressed 'per unit LBM'. Several of the reported series have included patients with malignant disease of differing types[2–5,7]. This adds to the problems of interpretation, and the practice of studying a defined 'pathological' population[6,8,9] is to be commended. Studies carried out under 'non-basal' conditions such as the postoperative period[4] or where unconventional expressions of tumour burden have been used[1] contribute to the difficulties in making comparisons between studies.

The present study of leucine kinetics has been carried out in a carefully defined group of patients requiring resectional surgery for benign or malignant disease of the large bowel. None of the patients gave a history of anorexia or weight loss. Isotope measurements were carried out after an overnight fast and there was no attempt to modify the voluntary nutritional intake in hospital. Tumour burden was defined according to the well established Dukes' classification plus an additional group with metastatic disease. The control group was important, and in this study control subjects were of similar age and undergoing surgery for benign colonic disease. Other studies have used laboratory volunteers[7] or patients who have had successful tumour resection as the control group[2], neither of which is ideal. One way of circumventing the problems of a control group is to carry out paired studies before and after the resection of a tumour[9]. Such a protocol is attractive but cannot be applied to patients with the more advanced tumours as there may be residual tumour even after surgical resection.

The present study shows no evidence of any alteration of leucine metabolism that might be attributed to the presence of a malignant tumour or that correlates with the estimated tumour burden. These conclusions support those made after investigations of patients with lung tumours[7], germ cell tumours[8] and in a previous study of adenocarcinoma of the colon[9]. Complexities of experimental design, heterogeneous patient populations and the use of unconventional or inappropriate methods of expression results may have contributed to the conflicting results previously reported.

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Salvage surgery for advanced local recurrence of breast cancer

D. Flook, D. J. T. Webster, L. E. Hughes and R. W. Mansel

University Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

Correspondence to:
Mr D. J. T. Webster

The development of myocutaneous flaps and other reconstructive procedures has made it possible to offer surgical palliation to many patients with advanced local recurrence of breast cancer who previously would have been regarded as untreatable. We present the results of excision of such recurrences in 42 patients treated from 1982 to 1986 after non-surgical measures had failed. Good palliation was achieved in all of the patients with acceptable morbidity. There was one death. Further local recurrences developed in 12 (29 per cent) patients, though none was painful or offensive. Thirteen patients remain alive and free from local disease; 17 patients remained free from local disease until they died.

Keywords: Breast cancer, local recurrence, surgery

Local recurrence after primary treatment of breast cancer may be only a minor problem in physical terms, but for a few unfortunate patients it becomes not just an unpleasant reminder of persisting disease but a progressive phenomenon leading to severe discomfort and deformity (*Figure 1*). The sheer size of the operative defect and difficulty in closing the axilla after excision of such tumours has often deterred surgical intervention in the past but with the development of myocutaneous and other local skin flaps it is possible to offer surgical treatment with primary wound closure to more of these patients.

We present our results of surgical treatment in patients with advanced local recurrence of breast cancer refractory to other forms of treatment.

Patients and methods

In the 5-year period from 1982 to 1986, 42 patients with painful or offensive local recurrence of breast cancer underwent radical excision of their breast or chest wall tumour, wound closure being aided by the use of either a rectus abdominis or latissimus dorsi myocutaneous flap, or a thoracoepigastric flap, with or without split skin grafting.

The mean age of the patients at the time of surgery for local recurrence was 56 years (range 28–86 years) and the mean period between primary treatment and salvage surgery was 4·5 years (range from 6 months to 26 years).

The primary treatment for breast cancer in these patients is shown in *Table 1*. The wide variation in treatment reflects the referral pattern to this secondary centre. There was wide variation in the stage at original presentation and in duration of disease.

Most of the patients received some form of treatment for their local recurrence before salvage surgery was contemplated. All but three of the 42 patients had undergone radiotherapy to the limits of local skin tolerance and, of these, 23 had also received hormonal treatment and 21 had received cytotoxic chemotherapy. In addition to progressive local disease, seven of the patients were known to have systemic metastases but were considered suitable for intervention because their distant disease was static or progressing slowly.

Local recurrences could be divided into two main forms: (1) patients with a single tumour mass, usually in a conserved breast, and (2) those who had infiltrating ulcerative tumours, a proportion of which were surrounded by multiple skin nodules (*Figures 2* and *3*). *Table 2* gives a summary of the range of tumour involvement and ulceration. In patients with multiple nodules, the largest diameter of clinically involved skin was recorded.

Surgical treatment for local recurrence entailed excision of all palpable tumour with a minimum margin of surrounding skin of 5 cm. In patients who had previously undergone conservative treatment, a Halsted mastectomy was performed tailoring the skin incision to the position of the recurrent tumour. For the remainder, the tumour was excised with underlying muscle and incorporating any ribs to which there appeared to be periosteal or bony fixation. In those patients who required rib resection and in whom the parietal pleura was breached (five cases), a chest drain was inserted and the chest wall defect was plugged with a portion of the muscle from the myocutaneous flap used for wound closure. Antibiotic prophylaxis was given as a single dose of metronidazole plus a cephalosporin at induction of anaesthesia.

Myocutaneous[1,2] and thoracoepigastric[3] flaps were raised according to techniques previously described and were sutured into the chest wall defect using chromic catgut or other absorbable sutures to anchor the muscle to chest wall, and interrupted silk sutures to the skin in early cases or subcuticular Prolene® (Ethicon Ltd., Edinburgh, UK) sutures later in the series.

Twenty-two latissimus dorsi flaps, 16 rectus abdominis and five thoracoepigastric flaps were employed to aid in wound closure, and in one patient split skin grafts alone were used. In one patient both a latissimus dorsi and a thoracoepigastric flap were required to obtain

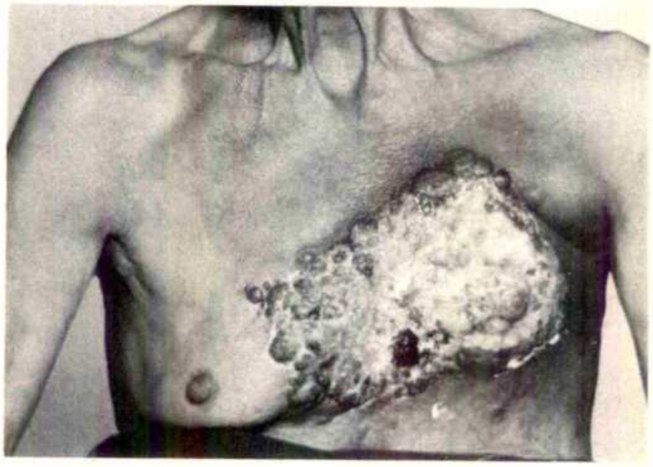

Figure 1 *An unpleasant fungating mass on the chest wall previously treated by radiotherapy, and subsequently chemotherapy. The patient declined surgery and died 15 months later with involvement of the whole chest and abdominal wall by tumour*

Table 1 *Primary treatment in 42 patients with local recurrence undergoing salvage surgery*

Radiotherapy alone	10
Radiotherapy and chemotherapy	11
Wide local excision and radiotherapy	5
Simple mastectomy and radiotherapy	1
Simple mastectomy alone	4
Patey modified radical mastectomy	3
Halsted mastectomy	2
Hormonal treatment alone	6

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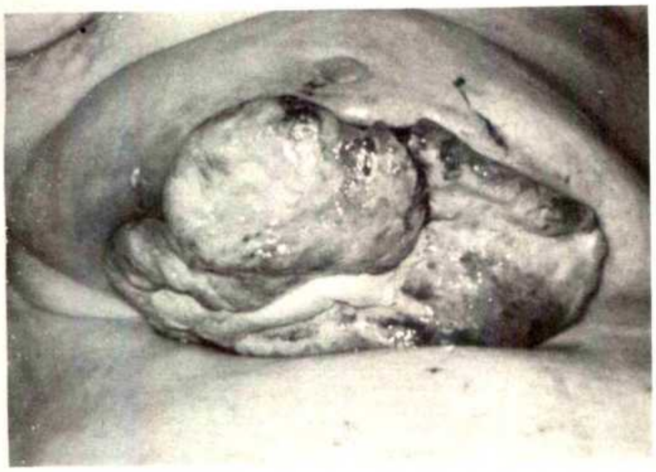

Figure 2 *An ulcerating breast lesion, neglected for 7 years, which did not respond to hormonal therapy or chemotherapy. In view of the large necrotic mass, surgery was preferred to radiotherapy as local treatment. The patient died from metastatic disease 15 months later*

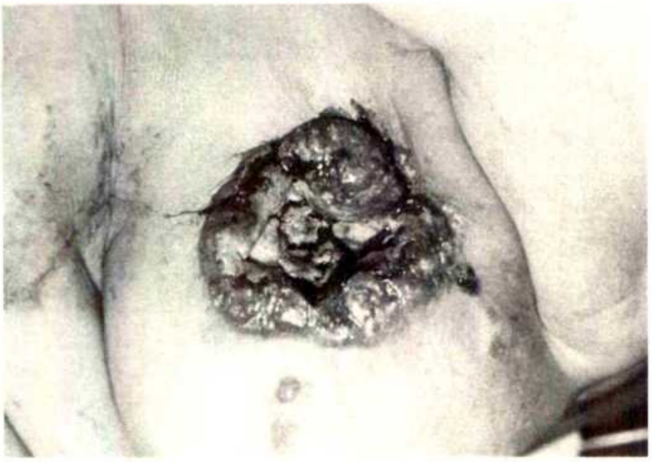

Figure 3 *An ulcerating mass with adjacent skin nodules following previous radiotherapy. After resection the patient remained free of local recurrence for 1 year and died 18 months after surgery from metastatic (pulmonary) disease*

complete skin cover, and in one further case a latissimus flap was used to replace a rectus flap which had failed. Three patients in the latissimus flap group, two in the rectus abdominis group, and one of the patients in whom a thoracoepigastric flap was employed required split skin grafting in addition because of the extent of the operative defect.

Results

Hospital stay and wound healing

Of the 42 patients in this series 30 required hospitalization for less than 3 weeks. In the 12 remaining cases hospital stay was prolonged to 4–16 weeks by delayed wound healing. Despite heavy preoperative bacterial colonization, wound infections were restricted to cellulitis which responded to antibiotic therapy; most of the delay in wound healing resulted from either failure of a portion of a skin flap or breakdown of a suture line involving previously irradiated skin under tension.

Complete wound healing was eventually achieved in all but two of the patients after salvage surgery. In the first of these, a mammary prosthesis inserted beneath a latissimus dorsi flap had to be removed because of infection, and the resulting wound was healing by granulation at the time of death only 3 months postoperatively. In the second case a suture line involving an area of previously irradiated skin dehisced, leaving a wide defect which was granulating and painless with a Silastic (Dow Corning, Reading, UK) foam dressing but which remained incompletely healed at the time of the patient's death 5 months after surgery.

Flap complications

Six patients (14 per cent) suffered complications relating to the skin flap; four of these (two rectus abdominis and two latissimus dorsi flaps) involved necrosis of the distal 25–30 per cent of the skin island, requiring excision and split skin grafting to the defect. The other two patients each initially had a rectus abdominis flap which underwent total necrosis, and in one of these cases the resulting defect (which included segments of two ribs) was covered with a latissimus dorsi flap. In this latter patient the skin island of the latissimus flap also necrosed although the muscle survived allowing later split skin grafting.

Other postoperative morbidity and mortality

With the exception of the wound problems already recorded, postoperative morbidity was limited to respiratory atelectasis or infection treated by mobilization, physiotherapy and antibiotics. No patient required intensive care after operation.

One patient died in hospital 4 weeks after salvage surgery, the cause of death being bronchopneumonia exacerbated by reactive depression and immobility.

Further local recurrences

Twelve of the surviving patients (29 per cent) developed further local recurrence after salvage surgery, although none of these recurrences was massive or painful. In three cases the further recurrence was limited enough to be excised locally. These patients remain alive; two of them are currently free from local disease.

Only two of the 17 (12 per cent) patients with a single mass of recurrent tumour developed further local disease after salvage surgery, but ten (40 per cent) of 25 patients with multiple tumour nodules suffered a further recurrence.

Survival after salvage surgery

Twenty-nine patients (69 per cent) died between 3 months and 6 years after salvage surgery (mean 1·6 years). Thirteen patients (31 per cent) remain alive 1–4 years after excision of local recurrence, and only one has evidence of chest wall disease at present.

Discussion

It is difficult to estimate the rate of local recurrences in the population from which these patients come as a wide variety of treatments is used in the region for both early cancer and advanced disease, and we presume that some patients have been treated by other surgeons. We have not treated surgically all those referred to us because we have thought the disease already too extensive or spreading so rapidly that early recurrence seemed inevitable—some patients have also declined the offer of surgery.

The options in the situation where the disease persists after previous radiotherapy, hormonal therapy and chemotherapy

Table 2 *Relationship of tumour and ulcer size*

	Ulcer size (cm)				
Tumour size (cm)	None	0–2	2–5	5–10	Total
0–2	—	—	—	—	—
2–5	2	1	5	—	8
5–10	7	1	6	3	17
10–15	4	1	5	2	12
15+	3	1	1	—	5
Total	16	4	17	5	42

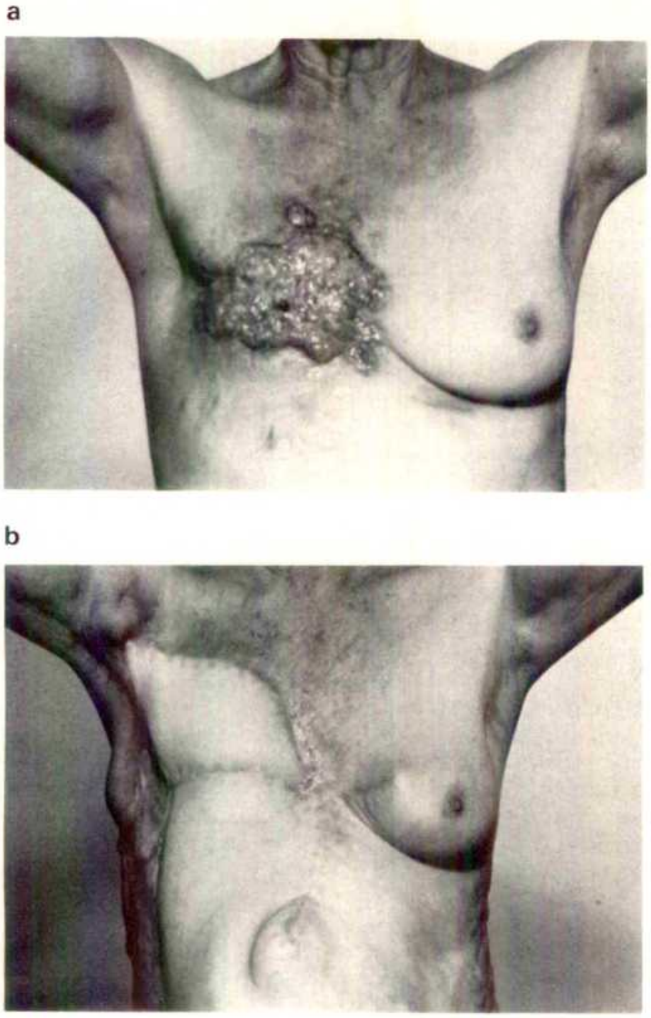

Figure 4 *Preoperative* (**a**) *and postoperative* (**b**) *views of a patient with extensive chest wall recurrence covered by latissimus dorsi and thoracoepigastric flaps. She developed further nodules around the periphery of the flaps 9 months later and died from disseminated disease 18 months after surgery*

are limited to palliative dressings, attempts to limit odour and surgery.

Our experience confirms that the use of myocutaneous flaps enables closure of the very extensive wounds resulting from excision of advanced breast and chest wall recurrences, with the particular benefit of the ability to cover any axillary defects. Otherwise, many of these defects could only have been covered by skin grafts or left to heal by granulation with the hazards of exposure of axillary structures and greatly prolonged wound healing.

The alternative approach[4], which we have not found necessary, is to place split skin grafts on to transposed omentum. This adds the risk of intra-abdominal complications as well as being cosmetically and functionally less acceptable to the patients.

The cosmetic results of our procedure were inevitably a compromise, but all patients showed an improvement from preoperative appearances (*Figure 4a* and *4b*) and none expressed regret at undergoing surgery.

The 25 per cent flap complication rate for rectus abdominis flaps (12 per cent partial plus 12 per cent total necrosis; four cases) and 14 per cent for latissimus dorsi flaps (9 per cent partial, 4 per cent total necrosis; three cases) encountered in this series are higher than we have experienced when employing these flaps for breast reconstruction after primary treatment of breast cancer[5]. Whilst these failures may have been partly related to the advanced age and poor general condition of patients undergoing salvage surgery, it is also possible that previous radiotherapy to the pedicle of a myocutaneous flap could have been involved in some of our complications. In particular, it was noted at the time of raising the only latissimus dorsi flap which underwent total necrosis that there was very marked axillary fibrosis following high-dose radiotherapy. Recently we have found Doppler ultrasound to be of value in confirming the patency of vessels in the flap pedicle before surgery.

The pattern of recurrence allows some prediction of subsequent outcome: patients with multiple intradermal nodules are more likely to develop further trouble than those with a large ulcerating solitary mass.

When local recurrence is likely, consideration of adjuvant therapy is appropriate but in such heavily pretreated patients an acceptable manoeuvre may not be available.

We feel that these results justify the decision to carry out extensive surgery in these patients with advanced locally recurrent breast cancer and would advocate the use of salvage surgery in any patient with distressing local disease who fails to respond to more conservative measures.

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Acute ischaemia of the upper limb compared with acute lower limb ischaemia; a 5-year review

P. A. Stonebridge, A. E. Clason, A. J. Duncan, B. Nolan, A. McL. Jenkins and C. V. Ruckley

Vascular Surgery Unit, The Royal Infirmary, Edinburgh, UK
Correspondence to:
Mr P. A. Stonebridge

A series of 61 patients with acute upper limb ischaemia treated over a 5-year period is analysed and compared with patients presenting with acute lower limb ischaemia during the same period. The mean age was 74 years with a female to male ratio of 2·2:1. Eighty-two per cent were treated by operation. Three patients died and no survivors required a major or minor limb amputation, in contrast to a 5 per cent major limb amputation rate in patients with acute lower limb ischaemia. Mortality for upper limb ischaemia was 5 per cent compared with a 30 per cent mortality rate in patients with acute lower limb ischaemia in whom cardiopulmonary debility (New York Heart Association score 3–4) was significantly greater.

Keywords: Acute upper limb ischaemia, acute lower limb ischaemia, morbidity, mortality

Acute ischaemia of the upper extremity is uncommon, accounting for only 15–18 per cent of acute ischaemic episodes of the extremities[1,2]. Nevertheless, when it does occur arm ischaemia may seriously jeopardize the livelihood and independence of the individual. Our recent experience of acute upper limb ischaemia in a regional vascular referral centre has been reviewed, and a comparison has been made with acute ischaemia of the lower limb.

Patients and methods

The medical records of patients presenting to the Vascular Surgery Unit of the Royal Infirmary of Edinburgh with acute upper limb ischaemia during the 5-year period 1983–87 were examined. The unit is a regional referral centre and serves a population of approximately 1·2 million. Patients were identified from ward discharge summaries, operating theatre registers and annual audit reports. Patients who presented with ischaemia after trauma or previous arterial reconstruction were not included in the study. Patients were treated either with conventional balloon catheter embolectomy or with intravenous heparin or thrombolytic therapy. A comparison with a previously analysed series of patients presenting with acute ischaemia of the lower limb in the same period was made.

Results

Sixty-one patients with acute ischaemia of the upper limb were identified with a total of 84 ischaemic episodes and compared with 204 patients presenting with acute lower limb ischaemia during the same period. The patient characteristics are shown in *Table 1*. Of the 61 patients with upper limb ischaemia nine patients experienced synchronous emboli to 12 other sites. Eleven patients were managed conservatively with either intravenous heparin or intravenous streptokinase, while 50 patients underwent operation. Three patients required additional synchronous vascular reconstructive procedures, two brachiobrachial vein bypass grafts for operative iatrogenic injuries and one axillobrachial artery polytetrafluoroethylene graft for an axillary artery stenosis. Eighty-seven per cent of patients received intravenous heparin and 79 per cent were treated with oral anticoagulants. Seven patients (11 per cent) had additional episodes of embolism while in hospital. Twenty patients (33 per cent) had a previous history of arterial embolus. Forty-three patients (70 per cent) had clinical evidence of a possible cardiac origin of the embolus (*Table 1*). The sites and levels of the ischaemic episodes are shown in *Table 2*.

Five of 25 echocardiograms performed showed intracardiac thrombus, but only one of these re-embolized, as did one in a patient with a negative scan. The outcome appears uninfluenced by the duration of symptoms, level of occlusion, pre-existing peripheral arterial disease, cardiopulmonary function (New York Heart Association (NYHA)) score* or recent myocardial infarction.

Table 1 *Patient characteristics*

	Upper limb	Lower limb
Total number	61	204
Average age (range)	74 (33–94)	70 (41–98)
Male:female	1:2·2	1:1·1
Atrial fibrillation (%)	64	65
Recent myocardial infarction (%)	10	11
Previous peripheral arterial disease (%)	20	67
Operation rate (%)	82	88
New York Heart Association score*		
1	20 (39)	19 (9)
2	12 (23)	65 (32)
3	13 (25)	85 (42)
4	6 (11)	32 (16)
Re-embolization rate	7 (11)	7 (3)
Amputation rate in survivors (%)	0	5
Overall mortality rate (%)	5	30

Values in parentheses are percentages. New York Heart Association score 1, no symptoms; 2, symptoms with more than usual activity, 3, symptoms with usual activity; 4, symptoms at rest. * Percentages are calculated from a total of 51 cases that were able to be scored

Table 2 *Anatomical details*

Side	Right. 37 (61)	Left: 23 (38)	Bilateral: 1 (2)
Site	Subclavian	10 (16)	
	Axillary	25 (41)	
	Brachial	23 (38)	
	Distal	2 (3)	

Values in parentheses are percentages

Only one factor was associated with a poor outcome and that was repeated embolism. Two of the seven patients with evidence of further recurrence died as a result of the further embolism (the third death was due to a pulmonary embolus), despite the fact that all were anticoagulated.

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* *NYHA score, a measure of cardiopulmonary debility according to the degree of symptoms of angina and/or breathlessness: class 1, no symptoms, class 2, symptoms with more than usual activity, class 3, symptoms with usual activity, and class 4, symptoms at rest*

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The mortality rate was 5 per cent (three patients), with a successful outcome (return to full function of the upper limb) in all 58 who survived.

Discussion

Acute ischaemia of the upper limb is uncommon (accounting for only 23 per cent of all cases of acute limb ischaemia in this study). In the present study 84 per cent of upper limb emboli were small enough to pass beyond the subclavian artery, but only 5 per cent of lower limb emboli reached the popliteal artery.

As in previous series[3–5] 70 per cent of patients had a possible cardiac origin for their embolus. All seven of those who had further emboli (11 per cent) were fully anticoagulated and fibrillating at the time of recurrence, while three had had a myocardial infarction within the two previous weeks. Ricotta *et al.*[4] reported a 33 per cent incidence of recurrence of embolism in patients who were not anticoagulated.

As previously reported[6,7] a higher mortality rate was found to be associated with re-embolization Therefore adequate anticoagulation of patients after embolectomy appears to be an important facet of management, and should not be based on the results of echocardiography, but rather on clinical assessment

Operative intervention for upper limb embolism has been shown to be superior to medical management[8] Even in an apparently viable limb the operative removal of an embolus is preferable in order to protect the proximal collateral supply on which the viability of the limb may depend

The low mortality in this series contrasts with the 12 per cent mortality rate due largely to cardiac causes which has been reported by other authors[5,6]. There were no cases of distal gangrene and no amputations were required, in contrast to patients with lower limb ischaemia in whom 5 per cent of survivors required amputations. Haemovici[5] in his personal series quotes a 78 9 per cent overall limb salvage rate, with a 7 per cent major amputation rate in survivors. The difference in morbidity may be due in part to a much higher incidence of proximal upper limb atherosclerotic disease. Ricotta *et al*[4] suggest an 18 per cent incidence of proximal disease in their series of upper limb ischaemia In this study proximal disease is a factor in only one of the 50 patients who underwent operation.

Comparison between upper and lower limb acute ischaemia (*Table 1*) reveals marked differences in terms of patient characteristics, morbidity and mortality. There are significantly fewer patients in the upper limb group who had evidence of generalized or localized occlusive arterial disease. There is a greater proportion of women with acute upper limb ischaemia. In the lower limb group there was a higher proportion of patients with severe cardiopulmonary symptoms although the average age of both groups was similar. The incidence of either atrial fibrillation or recent myocardial infarction was similar in both groups and it is reasonable to assume the incidence of cardiac emboli also to be similar. Differences in amputation rate have already been noted

The mortality rates are significantly different, with 5 per cent in the upper limb group and 30 per cent in the lower limb group ($\chi^2 = 15\ 4$, $P < 0{\cdot}001$). This may be accounted for by a number of factors: the size of the embolus, the presence of obliterative arterial disease in the lower limb group, and possibly a lesser risk of toxaemia on upper limb revascularization.

Our results show that operative treatment is a safe and effective means of management of acute upper limb ischaemia, the only contraindication to surgical treatment being a moribund patient or a limb beyond salvage.

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Incidence of septic and thromboembolic-related deaths after splenectomy in adults

W. Pimpl, O. Dapunt, H. Kaindl and J. Thalhamer

1st Surgical Department, Ludwig-Boltzmann Institute for Experimental and Gastroenterological Surgery, Landeskrankenanstalten Salzburg, Austria

Correspondence to:
Dr W Pimpl, I. Chirurgische Abteilung, Landeskrankenanstalten Salzburg, Muellner Hauptstrasse 48, A-5020 Salzburg, Austria

In a review of 37 012 autopsies over the last 20 years 202 deceased adults who had had a splenectomy were investigated. The incidence of infections and thromboembolic complications related to death in these patients was compared with that of a matched deceased population (n = *403) who had not undergone splenectomy. Death-related pneumonia was diagnosed frequently in the splenectomy group and to a lesser extent in the control group (57·9* versus *24·1 per cent,* $P<0{\cdot}001$*). Lethal sepsis with multiple organ failure occurred in 6·9 per cent of the splenectomy group and in 1·5 per cent of the controls* ($P<0{\cdot}001$)*. Purulent pyelonephritis was observed in 7·9 per cent of the splenectomy group and was significantly more frequent than in the control group with its rate of 2·2 per cent* ($P<0{\cdot}001$)*. Finally, pulmonary embolism was the major or a contributory cause of death more often in the splenectomy group than in the control group (35·6* versus *9·7 per cent,* $P<0{\cdot}001$)*. We conclude that splenectomy generates a considerable life-long risk of severe infection and of thromboembolism.*

Keywords: Splenectomy, thromboembolism, sepsis, autopsy

During the past decade, increased rates of early and late septic complications after splenectomy have been reported[1–7]. In 2–5 per cent of these cases a life-long risk of fatal sepsis has been assumed[8–18]. In addition, thromboembolic complications occur more frequently in asplenic individuals compared with a healthy population because of impaired platelet function[4,7,13,19]. These facts have encouraged attempts to repair the traumatically ruptured spleen or to preserve splenic function by reimplanting splenic tissue when splenectomy was unavoidable[20–29]. As some of these techniques require great technical skill and may extend the time of the operation, it can be harmful to attempt splenic preservation unless there are clearly defined benefits.

As there is still controversy in the literature concerning the risks of splenectomy, especially years after the operation, the optimal surgical management of ruptured spleen remains an open question. In order to define the true long-term risks of splenectomy, rather than examining complications of the early and late postoperative period, we have reviewed all autopsy records of the last 20 years at our institution to identify the causes of death in previously splenectomized adult patients and have compared these with a matched population. Legislation in our country ensures that nearly every patient who dies in our hospitals and those who die for unclear reasons at home have an autopsy. Therefore, and in contrast to other published papers, we should be able to define precisely the incidence of lethal postsplenectomy sequelae.

Patients and methods

The data were collected by retrospective review of 37 012 autopsies of adult patients who died in one of the six hospitals in Salzburg (a town with approximately 140 000 inhabitants) or who died at home for unclear reasons. Post-mortem examination of these patients was performed at the Institute of Pathological Anatomy (Professor Dr J. Thurner, Landeskrankenanstalten Salzburg).

The study series consisted of 202 adults (148 men, 54 women, mean age (± s.d.) 59·1 ± 15·9 years) who underwent splenectomy for various indications, as outlined in *Table 1*. The patients in the trauma group ($n=61$, 30·2 per cent) could be divided on the basis of three types of injury: isolated splenic rupture (type I), splenic injury plus thoracic trauma (type II) and splenic rupture plus head injury (type III).

The iatrogenic group ($n=63$, 31·2 per cent) comprised patients with splenic injuries sustained during abdominal surgery for non-malignant diseases.

Splenectomy for oncological reasons, such as gastric or colonic cancer, was performed in 56 patients (27·7 per cent).

In the final group, splenectomy was indicated because of haematological disorders ($n=22$, 10·9 per cent).

In order to evaluate postsplenectomy sequelae for the early postoperative period as well as for the later period, the patients were divided into two subgroups: those who died within 3 months of splenectomy and those who died more than 3 months after splenectomy.

As a control group we chose 403 patients (294 men, 109 women, mean age (± s.d.) 60·3 ± 16·6 years) who, during the same period, had comparable trauma or who underwent similar surgery for malignant or non-malignant diseases (*Table 1*).

In both groups, patients with lethal head trauma or exsanguinating injuries were excluded.

In our retrospective investigation we compared the incidences of the major causes of death in both groups. Furthermore, we tried to obtain information from the autopsy records about the rate of septic and thromboembolic complications with and without splenectomy. These specific complications have been chosen because their incidence has been reported to be more frequent in asplenic individuals[2,4,6,14,19].

In order to provide a good statistical comparison, special care was taken to ensure that the clinical data matched as well as possible. For the statistical comparison we used a two-tailed χ^2 test with Yates' correction (significance level, $P<0{\cdot}05$).

Results

Time period between splenectomy and death

One hundred and two (50·5 per cent) of the patients in the splenectomy group died within 3 months of the operation. A further 28·2 per cent of the patients died within the first three postoperative years. Subsequently, the number of deaths decreased as outlined in *Table 2*.

Major causes of death

The major causes of death are outlined in *Table 3*. In the splenectomy group the leading cause of death was pneumonia (50·5 *versus* 23·6 per cent in the control group, $P<0{\cdot}001$). Congestive cardiomyopathy, on the other hand, led to death significantly more often in the control group (29·3 *versus*

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Table 1 *Clinical characteristics of splenectomized patients and controls*

	Patients without spleen ($n=202$)	Patients with spleen ($n=403$)
Age (years, mean ±s.d.)	59·1±15·9	60·3±16·6
Sex		
Female (n)	54	109
Male (n)	148	294
Period between surgery and death		
Group 1 (<3 months)	102	222
Group 2 (>3 months)	100	181
Therapeutic subgroups (n)		
Trauma*		
Type I	25	46
Type II	26	55
Type III	10	22
Total	61	123
Iatrogenic (surgery for benign diseases)		
Nissen's fundoplication	7	12
Gastric resection	41	74
Colonic resection	13	34
Pancreatic resection	2	3
Total	63	123
Oncological (surgery for gastrointestinal malignancies)		
Gastrectomy	44	66
Colonic resection	6	37
Pancreatic resection	6	10
Total	56	113
Therapeutic (for haematological disorders)	22	44

*Type I, isolated splenic rupture (*versus* hepatic tears in the control group), type II, type I plus thoracic trauma, type III, type I plus head injury

8·4 per cent). In 16·3 per cent of the patients pulmonary embolism was lethal after splenectomy, compared with 4·7 per cent of the controls. This difference was highly significant ($P<0{\cdot}001$). In addition the incidence of sepsis was significantly higher in the splenectomy group ($P<0{\cdot}001$). In the control group advanced malignancies were significantly more often the major cause of death.

For all other specified causes of death, including myocardial infarction, there was no significant difference betwen the two groups.

Death-related complications

Severe pneumonia Severe pneumonia was diagnosed frequently in the splenectomy group and to a lesser extent in the control group (57·9 *versus* 24·1 per cent, $P<0{\cdot}001$; *Table 4*). A statistical difference between the two groups could be demonstrated for the whole series as well as for both early and late postoperative periods (*Table 5*) The rate of pneumonia was significantly higher in splenectomized patients in all disease subgroups with the exception of the therapeutic one (*Table 6*).

Sepsis. Lethal sepsis with multiple organ failure was diagnosed in 14 of 202 splenectomized patients (6·9 per cent), and was significantly more frequent than in the control group with six out of 403 patients (1·5 per cent; *Table 4*). Whereas the incidence of sepsis in the early postoperative period was similar in the two groups, after 3 months sepsis was more common in the splenectomized patients ($P<0{\cdot}001$; *Table 5*).

There were no statistical differences in the incidence of sepsis between the various disease subgroups, except the iatrogenic subgroup ($P<0{\cdot}03$; *Table 6*).

Purulent pyelonephritis. A purulent pyelonephritis was observed as the cause of death in 7·9 per cent of the splenectomy group, which was significantly more frequent than in the control group where it was 2·2 per cent (*Table 4*) Nearly all cases of pyelonephritis occurred in patients more than 3 months after splenectomy (*Table 5*). No statistical difference could be demonstrated for the subgroups between splenectomy patients and controls (except in the oncological subgroup; $P<0{\cdot}03$; *Table 6*).

Purulent meningitis Lethal meningitis was diagnosed in 0·5 per cent of the splenectomy group and in 1·0 per cent of the controls (difference not significant; *Table 4*).

Massive pulmonary embolism. Massive embolism of one, or even several branches, of the pulmonary arteries occurred significantly more often in splenectomized patients than in controls (*Table 4*). Furthermore, this statistical difference could be demonstrated for all investigated subgroups (*Tables 5* and *6*).

Discussion

In keeping with other published series our data show that splenectomy carries a considerable risk of infectious and thromboembolic complications, even years after the operation.

Concerning the major causes of death, our study identified that significantly more patients died from pneumonia, sepsis

Table 2 *Period between splenectomy and death in 202 patients*

Time period	n	%
<3 months	102	50·4
3 months to 1 year	26	12·9
>1–2 years	18	8·9
>2–3 years	13	6·4
>3–4 years	7	3·5
>4–5 years	4	2·0
>5–10 years	8	4·0
>10–25 years	24	11·9

Table 3 *Major causes of death for the whole series*

Cause of death	Patients without spleen ($n=202$)	Patients with spleen ($n=403$)	P
Pneumonia	102	95	<0·001
Pulmonary embolism	33	19	<0·001
Congestive cardiomyopathy	17	118	<0·001
Sepsis	14	6	<0·001
Myocardial infarction	10	25	>0·1
Cardiovascular accident	8	32	<0·09
Advanced malignancy	4	42	<0·001
Gastrointestinal haemorrhage	4	17	>0·1
Other causes	10	49	<0·01

Table 4 *Death-related complications for the whole series*

Complication	Patients without spleen ($n=202$)	Patients with spleen ($n=403$)	P
Severe pneumonia	117 (57·9)	97 (24·1)	<0·001
Sepsis	14 (6·9)	6 (1·5)	<0·001
Purulent pyelonephritis	16 (7·9)	9 (2·2)	<0·001
Purulent meningitis	1 (0·5)	4 (1·0)	>0·1
Pulmonary embolism	72 (35·6)	39 (9·7)	<0·001

Values in parentheses are percentages

Table 5 *Death-related complications with regard to the period between surgery and death*

	Patients dying <3 months after surgery			Patients dying >3 months after surgery		
Complication	Without spleen ($n=102$)	With spleen ($n=222$)	P	Without spleen ($n=100$)	With spleen ($n=181$)	P
Severe pneumonia	62	46	<0·001	55	51	<0·001
Sepsis	4	4	>0·1	10	2	<0·001
Purulent pyelonephritis	2	4	>0·1	14	5	<0·001
Purulent meningitis	0	4	>0·1	1	0	>0·1
Pulmonary embolism	34	18	<0·001	38	21	<0·001

Table 6 *Death-related complications with regard to indications for surgery*

	Trauma subgroup			Iatrogenic subgroup			Oncological subgroup			Therapeutic subgroup		
Complication	Without spleen ($n=61$)	With spleen ($n=123$)	P	Without spleen ($n=63$)	With spleen ($n=123$)	P	Without spleen ($n=56$)	With spleen ($n=113$)	P	Without spleen ($n=22$)	With spleen ($n=44$)	P
Severe pneumonia	41	27	<0·001	37	27	<0·001	30	35	<0·01	9	8	>0·09
Sepsis	4	1	>0·08	5	1	<0·03	4	3	>0·1	1	1	>0·1
Purulent pyelonephritis	2	0	>0·1	4	5	>0·1	7	3	<0·03	3	1	>0·1
Purulent meningitis	0	4	>0·1	0	0	>0·1	0	0	>0·1	1	0	>0·1
Pulmonary embolism	19	10	<0·001	22	12	<0·001	22	11	<0·001	9	6	<0·03

and pulmonary embolism in the splenectomy group than in the control group. No significantly higher incidence of myocardial infarction was found in the asplenic group. However, congestive cardiomyopathies and advanced malignancies were observed significantly more often in the controls.

With regard to the period between splenectomy and death, 50·4 per cent of the patients died within 3 months of the operation. The death rate decreased in the following years and was only 3·5 per cent in the fourth postoperative year. This observation is consistent with those of other authors[2,4,5,7] and may be due to the fact that many functions of the spleen are eventually balanced by other immunocompetent organs. Therefore, we can state that the highest risk of lethal sequelae after splenectomy can be expected during the first three postoperative years with a maximum in the immediate postoperative period.

Infectious complications

Most of the published series deal with infectious complications in the period immediately after splenectomy[1,2,4,7,22]. Infectious complications include urinary tract infections, pneumonia or sepsis, particularly operation-related sequelae such as wound abscesses or left-sided subphrenic collections. Francke *et al.*[2] described in their review a rate of 1–55 per cent of infectious complications and a mortality rate lower than 4 per cent. Obviously these rates are much greater in high-risk groups such as infants, immunocompromised patients or those with malignancies than in adults with elective splenectomy or splenectomy due to trauma[1,2,4,6,7].

In order to estimate the true risk of splenectomy it is therefore necessary to describe the morbidity and mortality with regard to the preoperative immunological status of the patient and the reason for the splenectomy. Ziemski *et al*[7] reported, in a recently published series comprising 688 splenectomized patients, overall morbidity and mortality rates of 51·1 and 4·7 per cent, respectively, for the early postoperative period. When the indication for surgery was taken into account, the mortality rate after splenectomy for trauma or primary benign splenic diseases was less than 1·0 per cent and increased to 8·4 per cent if the underlying disorder led to secondary hypersplenism. Left-sided pneumonia was observed most frequently in 20·4 per cent, which is comparable to other rates reported in the literature[1,4,7,22].

The rate of sepsis in the paediatric series ranged from 1·5 per cent (trauma) to 16·0 per cent (splenectomy for thalassaemia)[2,11,18]. Corresponding data for adults are much lower, revealing an overall mortality rate of less than 3 per cent for all indication groups[2,6,7,9,15,17].

In our series the most frequent cause of death within 3 months of splenectomy was pneumonia and the rate was almost three times higher than in the control group. Other infectious complications, within 3 months of splenectomy, were not observed to be more frequent in the splenectomized group compared with the non-splenectomized group.

Concerning late infectious complications after splenectomy, there are only a few reports in the literature and they comprise mainly data of postsplenectomy sepsis[1,2,4,7]. The main problem with these reports is that the periods of observation after splenectomy differ. Therefore the 'life-long' risk of splenectomy is still controversial. Furthermore, there exist only a few publications that compare splenectomized series with comparable control groups[1,11,27]. Carlstedt *et al*[1] described retrospectively a statistically higher rate of infectious complications in patients from whom the incidentally injured spleen had to be removed during abdominal operation than in a control group of patients undergoing proximal selective vagotomy with follow-up 8 years after the operation.

There exist only two prospective studies comparing the complications of patients after splenectomy with those of patients in whom the spleen could be salvaged. Green *et al.*[11] showed that the incidence of postsplenectomy sepsis in paediatric patients was 11 per cent in their small series of splenectomies, whereas the control group revealed no septic complications. Traub *et al.*[27] concluded in their recent report that reticuloendothelial function was better preserved after partial splenectomy than in autologous spleen transplantation, but that autotransplantation was superior to total splenectomy.

In the late postoperative period we demonstrated that the risk of severe pneumonia was two times higher in splenectomized patients than in the control group patients. The incidences of purulent pyelonephritis and of sepsis was also significantly higher in splenectomized patients than in the controls in the late postoperative period However, regarding the sepsis cases in our study, it is not possible to classify them as overwhelming post-splenectomy infection syndromes as this diagnosis cannot be established from a retrospective review of autopsy records without knowledge of the clinical course of the patients

Thromboembolic complications

Ziemski *et al* [7] published an incidence of pulmonary embolism in 3 per cent of patients during the early postoperative period after splenectomy. There have been no published comparative studies for thromboembolic complications in the late postoperative period since the extensive report of Robinette and Fraumeni[19], who did not show a significantly higher frequency of this complication in asplenic individuals. This fact is surprising, and contrasts with our results, as splenectomy causes a hypercoagulable state due to an increase of platelets in the peripheral blood count in the early postoperative period Several weeks after splenectomy the pooling of platelets occurs in other organs (e.g. liver), but a life-long relative increase of immature platelets in the peripheral blood may be responsible for thromboembolic disorders even years after splenectomy[29].

In our study pulmonary embolism was the most significant complication after splenectomy in all subgroups.

Myocardial infarction

In contrast to Robinette and Fraumeni[19] we did not demonstrate a significantly higher risk for myocardial infarction in the asplenic group compared with the controls This fact may be due to the small number of patients who survived for more than 3 months after splenectomy in our study.

Recurrence of gastrointestinal malignancies

In our series significantly more patients in the control group died from advanced malignancies compared with the splenectomy group. Unfortunately it is not possible to draw any conclusions about the rates of cancer recurrence in our patients from the autopsy records

Clinical consequences

In summary, we have to underline the opinion of Green *et al.*[11] that splenectomy can no longer be considered a safe operation. The following risks can be predicted. For elective splenectomy the overall risks of severe pneumonia and of pulmonary embolism can be estimated to be two and four times higher, respectively, than for a comparable operation without splenectomy Furthermore, there is a significant risk of lethal sepsis, even years after splenectomy. However, the highest rate (78·7 per cent) of these complications occurs within the first three postoperative years. Therefore, perioperative antibiotic prophylaxis (broad-spectrum penicillin plus aminoglycoside)[30] and preoperative pneumococcal vaccination[29] for patients of every age are advised. Exact preoperative diagnosis of the individual thromboembolic risk (history, concomitant diseases, laboratory tests, phlebography), perioperative intermittent compression boots, and heparin are strongly recommended. Postoperatively these patients should be encouraged to take a broad-spectrum penicillin and a low-dose aspirin for at least 3 years.

In cases of traumatic or incidental spleen injury during abdominal surgery, orthotopic spleen preservation should be attempted. Surgeons should choose the technique with which they are most familiar. In some cases, where the salvage of the massively ruptured spleen is not possible and when the abdomen is not contaminated, the reimplantation of splenic tissue into the greater omentum should be considered.

The patient who undergoes spleen autotransplantation should be treated in the same manner as the patient who has undergone splenectomy[24]. This includes long-term penicillin treatment as well as pneumococcal vaccination. The rationale for these requirements is the unreliability of autotransplants in the prevention of septic complications and the increase in antibody titres of pneumococcal vaccine seen in autotransplant patients[31].

We conclude that splenectomy carries an increased short- and long-term risk of both infectious and thromboembolic complications, and that whenever possible the procedure should be avoided.

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Short notes

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Operative mortality after perforated peptic ulcer

A. B. S. Ball, P. A. Thomas and S. J. Evans

Department of Surgery, Whipps Cross Hospital,
Leytonstone, London E11 1NR, UK
Correspondence to: Mr P. A. Thomas

The mortality rate associated with the surgical treatment of perforated peptic ulcer is reported to be under 10 per cent[1–3]. However, the Hospital In-patient Enquiry (HIPE) has revealed that the proportion of older patients (>60 years of age) admitted to hospital with a diagnosis of perforated peptic ulcer is rising[4]. A retrospective study of patients with perforated peptic ulcers who were operated on at Whipps Cross Hospital over a period of 3 years has been undertaken to examine the current age distribution of such patients and its relationship to the immediate postoperative prognosis.

Patients and methods

The medical notes of three consultants' patients undergoing surgery for perforated peptic ulcer between September 1984 and September 1987 were reviewed. Details of patients whose perforation was simply over-sewn and who died postoperatively were compared with those of patients in the same age group who survived with respect to 15 different variables (*Table 1*). Statistical comparisons were performed with Fisher's exact test. Differences were taken to be significant at the 5 per cent level

Table 1 *Variables included in analysis*

Age
Sex
Site of ulcer: gastric or duodenal ulcer
Duration of ulcer
Comorbid conditions*
Smoking status· smoker or non-smoker
Interval between perforation and surgery
Presence or absence of clinical shock†
Preoperative haemoglobin concentration
Preoperative white blood cell count
Preoperative haematocrit
Preoperative serum Na^+
Preoperative serum K^+
Preoperative blood concentration
Duration of surgery

* A medical condition other than peptic ulceration requiring medical supervision and/or admission to hospital within 3 years of ulcer perforation; † systolic blood pressure <100 mmHg and/or condition requiring preoperative central venous pressure line

Results

Between September 1984 and September 1987, 36 patients were operated on for perforated peptic ulcer (26 duodenal ulcers, ten gastric ulcers). More than half were ≥70 years of age. Eleven (31 per cent) died in the postoperative period (*Figure 1*)

Twenty-nine patients (81 per cent) underwent simple over-sewing of the perforation (*Table 2*). The median age of these patients was 72 years (range 19–91 years). Eight (28 per cent) died in the postoperative period (1–35 days after surgery). Four died from bronchopneumonia, two from septicaemia, one from myocardial infarction and one from acute renal failure The postoperative mortality rate of patients <70 years who underwent simple over-sew was zero compared with 47 per cent

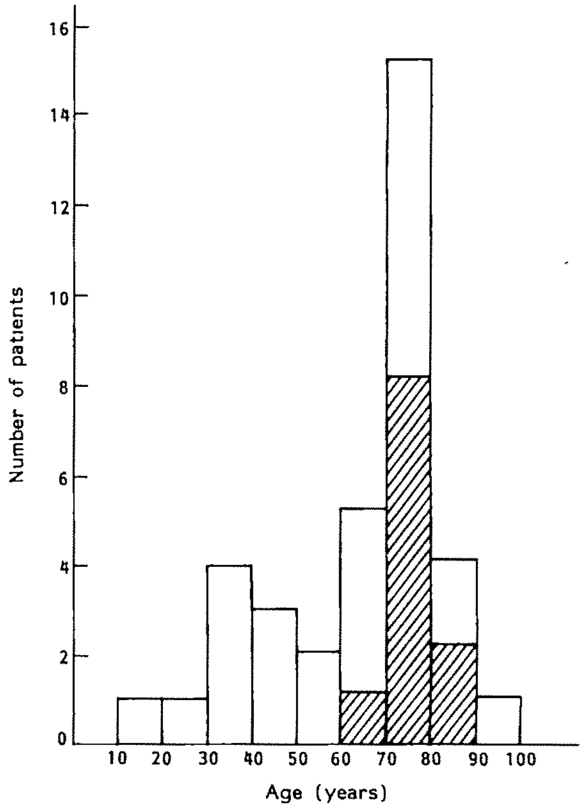

Figure 1 *Age distribution of mortality in 36 patients with perforated peptic ulcer.* ■, *Number of patients who died*

Table 2 *Characteristics of patients having simple oversew*

Age (years)	Sex: Men	Sex: Women	Duodenal ulcer	Gastric ulcer
<70	8	4	12	0
≥70	9	8	10	7

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in those $\geqslant 70$ years ($P<0{\cdot}02$). The patients <70 years old all had duodenal ulcers while 41 per cent of patients $\geqslant 70$ years had gastric ulcers ($P<0{\cdot}05$).

Among patients $\geqslant 70$ years of age who were clinically shocked on admission, the mortality rate after simple over-sew was 100 per cent compared with 25 per cent in those who were not shocked ($P<0{\cdot}02$) However, preoperative shock was only present in 63 per cent of the patients who died.

Among those patients $\geqslant 70$ years of age whose preoperative blood urea exceeded 15 mmol/l (twice the upper limit of normal), the postoperative mortality rate was 100 per cent compared with only 10 per cent in those with a lower blood urea ($P<0{\cdot}01$). Eighty-eight per cent of patients 70 years or older who died had a preoperative blood urea above 15 mmol/l while all the survivors had a lower blood urea preoperatively. There was no significant correlation between the age and the preoperative blood urea of patients in this study

There was no significant difference between the mortality rates of patients $\geqslant 70$ years with duodenal ulcers and that of patients $\geqslant 70$ years with gastric ulcers, and other variables such as the presence of comorbid conditions did not distinguish between patients $\geqslant 70$ years who died and those who survived

Discussion

The HIPE analysis indicates that the proportion of elderly patients admitted to hospital with perforated peptic ulcer is increasing[4]. This trend was evident in our series which revealed a high mortality among patients $\geqslant 70$ years with either duodenal ulcer or gastric ulcer even after simple over-sew. A similar observation among patients with perforated gastric ulcer has been reported recently[5]. Although the mortality of patients $\geqslant 70$ years was high, more than half survived, indicating that other factors contributed to mortality.

Preoperative shock was associated with a mortality rate of 100 per cent in patients $\geqslant 70$ years, but over a third of the patients who died were not clinically shocked on admission. A preoperative blood urea above 15 mmol/l in patients $\geqslant 70$ years was also associated with a postoperative mortality rate of 100 per cent but was present in a higher proportion (88 per cent) of those who died and was thus more specific.

It is unlikely that any single factor determines the outcome of surgery for perforated peptic ulcer. However, the identification of any group of patients in whom surgery is accompanied by an extremely high risk of postoperative mortality makes it important to consider alternative forms of treatment in these cases.

Conservative management for perforated peptic ulcer is now seldom undertaken. Nevertheless, previous studies have reported that the mortality rate with conservative treatment is remarkably low[6–9] Unfortunately, no studies have been properly controlled, and none has examined the role of conservative treatment specifically in elderly patients

This study suggests that there is a definable group of elderly patients in whom surgery is associated with a high risk of postoperative mortality In view of the increasing proportion of elderly patients admitted with perforated peptic ulcers, we suggest there is an urgent need to identify this group more precisely. If these patients can be accurately selected, the role of definitive, or preliminary expectant, conservative treatment in such cases should be re-evaluated

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Blood transfusion in colorectal cancer

M. C. Crowson, M. T. Hallissey, R. S. Kiff*, R. D. Kingston* and J. W. L. Fielding

*Surgical Immunology Unit, Queen Elizabeth Hospital, Birmingham and *Department of Clinical Studies, Park Hospital, Manchester, UK*

Correspondence to: Mr M. T Hallissey

Blood transfusion has been reported to improve graft survival following cadaveric renal transplantation as a result of an alteration in immunoresponsiveness[1]. Gant suggested that this effect may be detrimental to patients undergoing treatment for malignant disease[2]. Retrospective studies of perioperative transfusion have produced conflicting results[3–5].

Blood transfusion may simply be a marker of other recognized prognostic factors. To assess the effect of blood transfusion on the time to recurrence and duration of survival, independent of the known prognostic variables, a group of patients under prospective follow-up has been studied.

Patients and methods

The patients studied underwent surgery in hospitals in the West Midlands and North West regions of the UK between 1981 and 1983. All the patients were under the age of 80 years, had a modified Karnofsky score[6] of between 0 and 3 and had modified Dukes' B or C colorectal adenocarcinoma All operations were judged, by the operating surgeon, to be potentially curative. Data were collected prospectively for the recognized prognostic variables, as follows. age, sex, performance score, obstruction, heparin, site, Dukes' classification, histological grade, depth of penetration, circumferential involvement, haemoglobin at entry

Patients were followed up with full clinical and biochemical assessment every 3 months until death, or for 5 years Additional investigation for recurrent disease was undertaken when clinically indicated Tumour recurrence was diagnosed on clinical, radiological, ultrasound or pathological evidence of dissemination Time to recurrence and duration of survival were calculated from the date of resection

Blood transfusion details were obtained retrospectively by examination of the notes and blood transfusion records. The timing of

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Table 1 *Summary of significance values*

	All		Rectum		Perioperative	
	Recurrence	Survival	Recurrence	Survival	Recurrence	Survival
Log rank analysis						
Transfusion (P value)	0·63	0·57	0·68	0·15	0·88	0·78
Regression analysis						
Dukes' (P value)	<0·001	<0·0001	<0·0001	<0·0007	<0·0001	<0·0001
Sex (P value)	n.s.	<0·007	n.s.	n.s.	n.s.	<0·007
Age (P value)	n.s.	<0·006	n.s	<0·007	n.s	<0·006
Depth (P value)	<0·01	<0·01	n.s	n.s.	n.s.	<0·01
Blood transfusion (P value)	0·48	0·83	0·68	0·098	0·79	0·73

n.s., Not significant

transfusion was classified as preoperative (up to 30 days before surgery), perioperative (the 24 h during and after the operation) and postoperative

The effect of blood transfusion and the other prognostic factors have been assessed using log rank analysis To identify those factors having an independent effect on survival, a multiple regression analysis using Cox's method was performed Subset analysis has been undertaken by tumour site and timing of transfusion

Results

Of the 525 patients studied, 373 had received a blood transfusion and 152 had not. These groups were comparable for all the recognized prognostic variables. Only preoperative haemoglobin differed significantly between the two groups, being lower in the group receiving a transfusion ($P<0{\cdot}05$).

Log rank analysis showed no significant difference between the time to recurrence ($P=0{\cdot}63$) or overall survival ($P=0{\cdot}57$) in the transfused and non-transfused patients. Regression analysis identified Dukes' classification ($P<0{\cdot}0001$) and depth of penetration ($P<0{\cdot}01$) as the only factors to have significant independent effects on time to recurrence. Blood transfusion had no independent effect ($P=0{\cdot}48$). For survival, the age and sex of the patient together with Dukes' classification and depth of penetration of the tumour had independent effects ($P<0{\cdot}01$). Again transfusion had no significant effect on survival ($P=0{\cdot}83$).

Subset analysis by site or timing of transfusion failed to demonstrate any adverse effect of transfusion on either time to recurrence or survival. A summary of the levels of significance is shown in *Table 1*.

Discussion

The reports of the beneficial effect of blood transfusion on renal allograft survival[1] prompted Gant to suggest that this effect may adversely affect patients with malignant disease[2]. Two retrospective clinical reviews have reported an effect of blood transfusion on both the time to recurrence and survival following resection of lung, breast and colorectal cancer[3,4]. In colorectal cancer, one study[3] has suggested that transfusion is second only to pathological stage as a prognostic indicator, while in others the tumour site[4] and operative transfusion were critical to identifying any effect.

The present study has failed to demonstrate any adverse effect of blood transfusion either on the time to recurrence or on survival and these have been shown to be independent of the time of transfusion and the site of the tumour. This concurs with the results from Nathanson *et al.*[5] who showed that transfusion had an adverse effect when considered in isolation. However, this effect was lost when a regression analysis was performed. Frankish *et al.*[7] have also failed to show an effect in a prospective study, which has a 3-year follow up.

It has been suggested that blood transfusion should be avoided in patients with malignant disease because of its adverse effect on survival The present study does not support this opinion.

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Paper accepted 9 December 1988

Correspondence

Low molecular weight heparins and prevention of postoperative thrombosis

Sir

Two studies on the prevention of postoperative deep vein thrombosis (DVT) with low molecular weight heparin (LMWH) fractions have been published recently in *The British Journal of Surgery*. They deserve a few comments.

Although both trials claim superiority of the LMWH compound over standard heparin, 'intention to treat' analysis of the data reveals that this superiority is not statistically significant at the conventional P level of 0·05. In the Scandinavian study using Fragmin® (Kabi Vitrum, Stockholm, Sweden) (*Br J Surg* 1988, **75** 888–91), 28 isotopic DVTs (5·5 per cent) were detected in the LMWH group compared with 41 (8·3 per cent) in the standard heparin group ($P=0\cdot08$, two-sided test). The corresponding figures in the European Fraxiparin study (Sanofi Choay, France; *Br J Surg* 1988, **75** 1058–63) are 29 isotopic DVTs (3·0 per cent) in the LMWH group and 41 (4·4 per cent) in the standard heparin group ($P=0\cdot14$ two-sided Fischer exact test).

The analysis presented in the European Fraxiparin Study paper with correction of the isotopic DVT rate by integrating phlebographic data obtained in only 39 per cent of the cases with abnormal fibrinogen uptake test is not acceptable, especially because the study was not double-blind. Moreover, using a two-sided test, which is obviously more appropriate than the one-sided one when comparing two active treatments, reveals no significant difference between the two groups ($P=0\cdot065$), even with the corrected data. Thus, the two trials confirm and extend previous work showing that injection of a LMWH fraction once daily is at least as efficient as injection of standard heparin twice a day (Scandinavian study) or three times a day (European Fraxiparin Study) in general surgery. Bleeding complications also seem to be at least as frequent with LMWHs.

In the era of AIDS, these trials raise also the question of the safety of the fibrinogen uptake test as regards risk of virus transmission. In my opinion, injecting a blood derivative in asymptomatic patients for screening purposes should be seriously questioned. Possibly liquid crystal contact thermography which has a similar sensitivity and specificity in postoperative subjects[1] might represent an attractive alternative to the fibrinogen uptake test.

H. Bounameaux

University Hospital of Geneva
Geneva
Switzerland

1 Pochaczevsky R, Pillari G, Feldman F. Liquid crystal contact thermography of deep venous thrombosis. *Am J Roentgenol* 1982, **138**· 717–23

Authors' reply

Sir

The comments made by Dr Bounameaux are relevant and we are grateful to be able to answer.

We have given the data on intention to treat in our Results section in exactly the same way as Dr Bounameaux. In our protocol we made a biostatistical calculation to also be able to analyse patients who had been given correct prophylaxis as defined in the protocol. This is described in detail in the methodological section of our paper. Therefore we have given data both on the basis of intention to treat and on the basis of correctly treated patients. This is perfectly clear from our paper.

Dr Bounameaux has missed one important point in our study, which was new when we started it· the first dose given in the evening before surgery, which also contributes to the practicability.

Nowhere in our paper have we drawn any conclusion about a lower risk of bleeding with low molecular weight heparin. On the contrary, we stated, 'A disadvantage is the slight increase in haemorrhagic side effects, even though the bleeding episodes were of minor clinical importance.'

One important concern is the potential risk of virus transmission with fibrinogen used for diagnoses in the fibrinogen uptake test. When this risk became evident our study was stopped until the manufacturers could give a reasonable guarantee concerning their product, that is very few, reliable donors who repeatedly have negative HIV tests. Obviously a completely non-invasive test would be preferable but none exists today with the sensitivity of the fibrinogen uptake test. The suggestion of thermography based on the study by Pochaczevsky *et al*[1] seems less well founded as these authors compared phlebography and thermography in only 30 patients with suspicion of deep vein thrombosis. On the contrary, in postoperative patients the agreement with fibrinogen uptake test for screening was not as good and decreased when thrombi were localized distally[2]. With careful selection of fibrinogen donors this test remains the method of choice, at least in non-orthopaedic patients.

D. Bergqvist*, T. Mätzsch, U. S. Burmark, J. Frisell, O. Guilbaud,
T. Hallböök, A. Horn, A. Lindhagen, H. Ljungnér, K. G. Ljungström,
H. Onarheim, B. Risberg, S. Törngren, P. Örtenwall

** General Hospital*
S-214 01 Malmö
Sweden

1. Pochaczevsky R, Pillari G, Feldman F. Liquid crystal contact thermography of deep venous thrombosis. *Am J Roentgenol* 1982; **138**. 717–23
2. Bergqvist D, Hallböok T. Thermography in screening post-operative deep vein thrombosis: a comparison with the ^{125}I-fibrinogen test. *Br J Surg* 1978, **65**. 443–5.

Author's reply

Sir

The letter of Dr Bounameaux deserves a few comments. The European Fraxiparin Study data were evaluated on the basis of intention to treat. Dr Bounameaux's statement that it would have been more appropriate to have used a two-sided rather than a one-sided statistical test to analyse the results is not obvious, especially since the form of analysis was chosen before the start of the study, and the number of patients probably required was based on this calculation.

The use of heated fibrinogen may minimize the risk of virus transmission using the fibrinogen uptake test. There are several reasons in favour of replacing this test, but none of the possible alternatives has been sufficiently tested so far.

K. Breddin

Klinikum der Joh.-Wolfgang-Goethe Universitat
Frankfurt
FRG

Suction drains

Sir

Having read the article by A. Stacey-Clear and R. M. Hiddle (*Br J Surg* 1988, **75**. 1195), I would like to point out two faults with the method suggested by the authors for securing suction drains.

First, as the drain is not fixed at its point of exit, it is free to move in and out. This is more likely if the space or cavity being drained is large and there is sufficient length of drain between the tie and the point of exit. If the cavity is sterile, this movement from outside to inside is undesirable.

Second, as the tie passes through the drain and through the skin, it converts a closed system to an open one.

With good surgical technique using a strong braided suture and careful nursing, there is no reason why a drain, secured in the traditional way, should fall out.

N. Briffa

Manchester Royal Infirmary
Manchester M13 9WL
UK

Endoscopic sphincterotomy

Authors' reply

Sir

We were interested to read the letter from Messrs Bickerstaff, Chapman and Britton (*Br J Surg* 1989; **76**: 316) and their criticism that we had not referred to the four papers that they quote. In fact we did refer to the previously published paper in the *The British Journal of Surgery*[1]. We were also aware of the other three papers but did not feel that two[2,3] were worthy of discussion as they were reports of very small numbers of patients (five and 16, respectively).

In such small series it is not surprising that the authors were able to report 100 per cent success and no complications or deaths, results unlikely to be borne out by greater experience. We were also aware of the fourth paper they mentioned[4] but found ourselves in some difficulty interpreting the results. This paper is not confined to endoscopic sphincterotomy for retained bile duct stones and within it there are certain discrepancies. It is stated that 76 patients underwent this procedure, but later the authors refer only to 75 patients, claiming successful clearance of the duct in 72 (96 per cent). They state that there were no complications but mention without qualification that in one patient, a basket broke in the bile duct. We are not informed what happened to this patient or to the two patients in whom the stones could not be extracted

We emphasize that we have reported a 30-day mortality rate but it is not apparent whether this was so in the papers quoted One of our patients died following surgery for an impacted basket and another following surgery for unsuccessful endoscopic clearance of the bile duct Our complication rate was 12 per cent if occult haemorrhages are excluded (not 15 per cent as suggested). We remain cautious about endoscopic removal if other alternatives which are less hazardous but equally successful are available.

The early recourse to endoscopic retrograde cholangiopancreatography and sphincterotomy proposed by Bickerstaff *et al.* is surely premature; many patients with small stones retained after exploration will pass their stones spontaneously if left without interference We consider it unwise to perform early, possibly unnecessary, endoscopic sphincterotomy simply to allow removal of the T tube.

In view of the last sentence in their letter we should like to point out that it was exactly the philosophy that it might be safer to leave stones behind for later endoscopic removal that was adopted in the morbidly obese 43-year-old man with cholangitis and jaundice, and ultimately an impacted basket, who died.

D. E. F. Tweedle
D. Martin

University Hospital of South Manchester
Manchester M20 8LR
UK

1 O'Doherty DP, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for retained common bile duct stones in patients with T-tube *in situ* in the early post-operative period *Br J Surg* 1986; **73**: 454–6.
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Rectus abdominis muscle flap

Sir

We read with interest the recent report by Young *et al.* (*Br J Surg* 1988; **75**. 1228) We have recently used a rectus abdominis muscle flap to try to heal a persistent perineal sinus, but have met with limited success.

A 31-year-old man presented with a perineal sinus following panproctocolectomy for longstanding ulcerative colitis. The sinus, present for 2 years, was associated with low back pain, a variable urinary system and difficulty gaining and maintaining full erection Occasionally small bowel contents were thought to be discharged At a subsequent laparotomy, left psoas and pelvic abscesses were drained and a small bowel fistula divided from the pelvic diaphragm and repaired.

One year later, the perineal sinus/fistula recurred, together with left loin pain, ill health and weight loss. At laparotomy, a large left loin abscess was drained and a rectus abdominis muscle flap based on the inferior epigastric pedicle was transposed to lie in the pelvis A pelvic suction drain was used and the anterior abdominal wall was closed with polydiaxonone sutures No attempt was made to repair the posterior rectus sheath and the deformity is negligible

One month postoperatively, the perineal wound continued to discharge. Six months later, bilateral gracilis muscle flaps were transposed to the posterior pelvic cavity, resulting in perineal healing. Suction drainage was again used in the early postoperative period. There has been no recurrence of the sinus in the 6 months since the operation The patient's urinary system and sexual function have returned to normal and there has been no loss of function secondary to the use of these three muscle flaps

This case suggests that the rectus abdominis flap was successful in controlling the fistulation tendency and probably filled the upper part of the cavity. This left a space which was well managed by the standard gracilis transposition procedure, which offers a useful additional flap(s) with little or no postoperative morbidity The use of suction drainage of the muscle flaps and pelvis as described in the case report would seem to be important.

N. D. Heaton
A. W. Clark

Royal Sussex County Hospital
Brighton BN2 5BE
UK

Endoscopic treatment of acute biliary pancreatitis

Sir

Mr Neoptolemos and his colleagues have clearly demonstrated that the systemic use of urgent endoscopic retrograde cholangiopancreatography (ERCP) during attacks of acute pancreatitis is a valuable method for the detection of common bile duct stones (*Br J Surg* 1988, **75**: 954–60) If stones are found, endoscopic sphincterotomy should be performed. Neoptolemos *et al.* reported a 19 per cent overall complication rate and a 2 per cent mortality rate of this technique in gallstone pancreatitis

Endoscopic sphincterotomy is not generally accepted as the first method in the treatment of acute biliary pancreatitis. It is therefore of interest to evaluate the efficacy of endoscopic sphincterotomy in acute pancreatitis due to gallstones. This was done by an international survey of the procedures performed in 19 middle-European endoscopic departments[1]

In this collected series, out of 11 830 endoscopic sphincterotomies, 261 (2·2 per cent) were performed in patients with acute biliary pancreatitis All of the sphincterotomies were done within 48 h The bile duct stones were shown during endoscopic retrograde cholangiography.

The endoscopic procedure was successful in 236 (90·4 per cent) cases out of the 261 patients. Complications developed in 13 patients (5·5 per cent) haemorrhage in eight patients, pancreatic necrosis in four cases and sepsis from biliary origin in one patient. Surgery was needed in four cases.

The mortality rate was 1·9 per cent The cause of death was pancreatic necrosis in four cases and biliary sepsis in one patient

The results of our international survey show that endoscopic sphincterotomy is a safe procedure in the treatment of acute pancreatitis due to gallstones.

The participants of the survey were: Austria, P. Kratochvil, W. Weiss; Czechoslovakia, S. Safar, A. Vavrecka, GDR, R. Arendt, H Bosseckert, K.U. Schentke, E Schwenke, D. Wöstenberg, Hungary, Z. Dobrónte, I.E Farkas, L Juhasz, G. Kalasz, I. Malyi, I. Papp, I Rácz, L Simon, Z Szabó, I. Szanto, Z. Tulassay; Poland, A Nowak, Yugoslavia, I. Krizman.

Z. Tulassay
I. E. Farkas

Semmelweis University
H-1083 Budapest
Hungary

1 Farkas IE, Tulassay Z, Papp J. Endoscopic sphincterotomy in acute biliary pancreatitis. results of an international survey (abstract). *Digestion* 1988, **40**: 80.

Definitive one-stage emergency large bowel surgery

Sir

Mr Mealy and his colleagues (*Br J Surg* 1988; **75**. 1216–19) decided, in electing to treat obstruction and perforation of the large bowel by immediate resection of the diseased segment, that they would also 'avoid a colostomy except for compelling reasons' While welcoming their report, we would like to comment on their conclusions

There is now a considerable measure of agreement on the management of neoplastic large bowel obstruction. Right hemicolectomy is now the standard treatment for obstruction in the proximal colon, and, increasingly, extended right hemicolectomy[1] with immediate ileocolic anastomosis is used for neoplasms in and just beyond the splenic flexure; a stoma is hardly ever needed. With increasing use of intraoperative colonic emptying it is possible to carry out immediate resection and a safe restorative anastomosis on lesions obstructing the left colon, and here our policy[2] and that of Mealy and his colleagues appears to be similar. They performed primary anastomosis in 25 of 31 patients (81 per cent) with a left colon obstruction, compared with our figure of 47 anastomoses in 52 patients (90 per cent) In both series the mortality rate was around 10 per cent, most deaths being due to intercurrent disease

However, caution must be exercised in suggesting so definitely that this type of surgery can be carried out by registrars – a term which embraces trainees with widely differing degrees of experience. The most careful judgement must be exercised when deciding whether these elderly and often unfit patients will benefit from an operation which takes longer and can carry a higher risk, and the operator must already have considerable experience of elective colonic resection. The large series from the Large Bowel Cancer Project[3] is not reassuring about the results achieved by registrars in this field, and the CEPOD report[4] is a reminder of the lack of supervision which can prevail. In this field, everything depends on the expertise and advice available at the time of operation.

We have serious misgivings about the promotion of a deliberate policy to avoid a stoma when treating colorectal perforations. In assessing such a policy it is important to be careful about the use of the term 'peritonitis'. *Table 2*, which analyses 'pathological grade of peritonitis' in 68 patients undergoing laparotomy, shows that 36 (53 per cent) had localized inflammation without pus in the peritoneal cavity. In some of these patients it might have resolved under conservative management[5], and certainly it would be wrong to draw any conclusion about the safety of anastomosis in the presence of peritonitis from the results in this group. Sixteen of 26 patients with generalized peritonitis had a resection with anastomosis, but the outcome is not known. In the 36 patients in our study[2] who had a primary resection for colonic perforation with purulent of faecal peritonitis, only 12 had an anastomosis as it was thought safer to make an end stoma in 24: there were two deaths (5·5 per cent). Ryan[6] was a keen advocate of resection and anastomosis for perforated sigmoid diverticulitis, but he only used this method in half his patients, and advised caution in the presence of diffuse peritonitis.

Although there is a strong surgical tradition that there is a greater risk if a colonic anastomosis is made in the presence of peritonitis, there is no firm clinical evidence to support this belief. However, there are two good reasons for exercising caution. One is that these patients are often already toxic and ill, and may not be well served by an operation taking an extra 45–60 min. The other reason is that there are very few reports of emergency anastomosis of the colon without the occurrence of some subsequent leaks from the suture line (overall incidence was 8·4 per cent in the series of Mealy *et al*, and 6·6 per cent in ours). It is doubly unfortunate if this complication occurs in a patient who is already suffering from diffuse peritonitis, even though it may be resolving.

We believe, therefore, that it is most unwise to state in the summary, without qualification, that 'resection and primary anastomosis can be performed with acceptable morbidity and mortality in a high proportion of large bowel conditions, irrespective of ... the presence of peritonitis'.

P. F. Jones
N. M. Koruth
Z. H. Krukowski
A. Munro

University of Aberdeen
Aberdeen AB9 2ZD
UK

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6. Ryan P. Emergency resection and anastomosis for perforated sigmoid diverticulitis. *Aust NZ J Surg* 1974; 16–20.

Authors' reply

Sir

We appreciate the interest and comments of Professor Jones and colleagues from Aberdeen on our paper.

We fully support the contention that emergency large bowel surgery is exacting and requires good judgement and operative experience. Furthermore, we did note the recent CEPOD report and acknowledge that close co-operation between registrars and their consultant colleagues is essential.

The decision to operate or to manage conservatively localized inflammation of the colon is difficult. We agree that little can be inferred from the results of primary anastomosis in this group. For this reason we carefully defined the degree of peritonitis in a similar manner to that previously reported by the Aberdeen group. One death occurred in our group of 16 patients with generalized peritonitis who underwent a resection and primary anastomosis (6·25 per cent). This was due to multiple organ failure in a 54-year-old woman with lymphomatous perforation of her sigmoid colon. Of interest is the fact that one of four patients with generalized peritonitis who had a Hartmann procedure also died.

We also agree that caution is required in performing a primary anastomosis in these groups of patients. However, we believe that in many cases it takes little longer to perform a left colonic resection and anastomosis than to perform a Hartmann procedure, most now accept the need to resect the inflammatory lesion at initial operation. We re-emphasize that our intraoperative colonic evacuation takes approximately 10 min.

We feel that our conclusions were qualified and are justified by demonstrating that a high proportion of large bowel conditions can be managed in this fashion.

K. Mealy
A. Salamn
G. W. Arthur

Worthing District Hospital
West Sussex BN11 2DH
UK

Acute lower limb ischaemia

Sir

We read with interest the recent paper by Walker and Giddings (*Br J Surg* 1988; **75**: 1189–92) on the treatment of acute lower limb ischaemia using intra-arterial streptokinase. They suggest that this treatment is particularly useful in three situations, namely, acutely thrombosed popliteal aneurysms with tibial artery thrombosis, thrombosis of an autogenous vein graft and embolization of a cardiac thrombus following acute myocardial infarction. Streptokinase may also be of value in patients with non-acute ischaemia, as relatively fresh thrombus may be found within an atheromatous occlusion.

We have treated 11 consecutive patients with chronic lower limb ischaemia due to arterial occlusions apparently not suitable for either vascular reconstruction or angioplasty. Seven patients had rest pain, and four had incapacitating intermittent claudication of more than 1 month's duration. We used a technique similar to that of Walker and Giddings but with a higher dose of streptokinase (20 000 units/h) for between 18 and 72 h. In four patients the vessel was cleared sufficiently to allow successful angioplasty, with clinical, radiological and Doppler pressure improvement. One patient had considerable dissolution of thrombus, but angioplasty was still not possible. One patient subsequently underwent femoropopliteal bypass grafting, having had no objective improvement from streptokinase, only one patient required an amputation. All but the last patient had some subjective benefit. Three patients developed haematomas, the streptokinase infusion being terminated in one and temporarily discontinued in another. In one patient there was slight derangement of clotting (INR 1·8).

Streptokinase is clearly less effective in chronic compared with either acute or subacute ischaemia. Nevertheless, we feel that for those patients with severe symptoms who are not suitable for either reconstruction or angioplasty, intra-arterial streptokinase should be considered as even partial clearance of the vessel may permit subsequent successful intervention.

M. J. R. Lancashire
B. W. Williams
E. P. H. Torrie
R. B. Galland

The Royal Berkshire Hospital
Reading RG1 5AN
UK

Lower gastrointestinal bleeding

Letter 1

Sir

In his leading article 'Lower gastrointestinal bleeding', Mr Spencer (*Br J Surg* 1989; **76**: 3–4) failed to mention the technique of intraoperative colonoscopy with antegrade colonic irrigation[1]. We believe this procedure to be an important recent development in the diagnosis and treatment of major colonic haemorrhage. Although mesenteric angiography and radioisotope scanning can undoubtedly be helpful in moderate or intermittent bleeding, they have little place in the management of major colonic haemorrhage, may cause a dangerous delay to urgent surgery, and are less likely to reveal the precise site of bleeding than intraoperative colonoscopy[2].

It is disturbing to read in 1989 that blind colonic resection, subtotal colectomy and the formation of a transverse colostomy should still be advocated. In an extensive review of the literature[3] we found that blind colectomy in patients with major active lower gastrointestinal bleeding was associated with an unacceptable rebleeding rate of approximately 30 per cent and a mortality of 20–40 per cent. Accurate localization of the site of haemorrhage allows an appropriate limited resection and should be the aim of the surgeon when treating patients with life-threatening haemorrhage. This can and should be achieved by early operation and intraoperative colonoscopy with antegrade colonic irrigation.

A. R. Berry
M. G. W. Kettlewell

John Radcliffe Hospital
Oxford OX3 9DU
UK

1. Campbell WB, Rhodes M, Kettlewell MGW. Colonoscopy following intraoperative lavage in the management of severe colonic bleeding. *Ann Roy Coll Surg Engl* 1985, **67**: 290–2
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Lower gastroinestinal bleeding
Letter 2

Sir

While agreeing with much of Mr Spencer's review of lower gastrointestinal haemorrhage (*Br J Surg* 1989, **76**: 3–4), we were disappointed that there was no mention of localizing bleeding by isotopic methods. The advent of *in vivo* labelling of red blood cells with technetium-99m has provided a simple yet elegant investigation[1] which should be considered as well as arteriography and colonoscopy. The main disadvantage of angiography is that there must be active bleeding at the time of contrast injection for the investigation to succeed. Scintigraphic detection of bleeding does not have this limitation because extravasated radiolabelled red blood cells accumulate at a bleeding site and can be detected by scanning which may be delayed by up to 36 h after the injection of isotope. This feature, along with the ability of scintigraphy to detect lower bleeding rates (0.05–0.1 ml/min)[2] than angiography (0.5–1.0 ml/min)[3], make it particularly suitable for the investigation of lesions which bleed slowly and intermittently.

Over a 3-year period we have performed 43 isotope scans in 41 patients with lower gastrointestinal haemorrhage, the investigation proving to have a sensitivity of 97 per cent and a specificity of 85 per cent[4]. We found that the investigation was particularly useful in localizing the bleeding point to either one side or the other of the colon in cases of angiodysplasia and diverticular disease. Of the 12 large bowel resections performed only one was a subtotal colectomy.

Red cell scanning will not provide all the answers in cases of lower gastrointestinal bleeding but our experience suggests that it deserves further study and more widespread use.

M. L. Nicholson
D. P. Fossard

Leicester Royal Infirmary
Leicester LE2 7LX
UK

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Organ donation

Sir

The paper by Wakeford and Stepney (*Br J Surg* 1989, **76**: 435–439) is a commendable attempt to identify the obstacles to organ donation by surveying the attitudes of the general public and the medical and nursing professions. Unfortunately, they have failed to identify any obstacles and in consequence their recommendations for increased training of staff and education of the public are bland, unsupported by their own evidence, and almost certainly useless.

Intensive care unit staff were invited to indicate which of nine factors they saw as restricting organ harvesting in their own units. None were thought to be definitely important by even a quarter of those responding. Why then are more donors not being referred? Lack of training in how to approach relatives was thought definitely to be a factor by only 4 per cent of the doctors whose task it should be to make such approaches. Education and advice on transplantation would apparently be valued by only 25 per cent of the general public while 35 per cent expressed antipathy to the suggestion. It would be remarkable if training of those who see no need for it and education of those who do not want it achieved the desired aim of increasing the supply of organs for transplantation.

If organ supply is to be improved we need to know why all suitable donors are not being offered to transplant teams at present. Three questions which the authors could have asked intensive care unit staff might have provided interesting answers.

1. How many potential organ donors have you treated in the last year?
2. How many were referred for organ donation?
3. What were the reasons for non-referral in each case?

If truthful answers were given we could at least discover the reasons why so many usable organs are currently wasted. We need to know the real answers to these questions so that effective recommendations can be made to increase the present inadequate supply of organs for donation.

J. Collin

John Radcliffe Hospital
Oxford
UK

Partial fundoplication after abdominal Heller's myotomy

Sir

The publication by Crookes *et al* (*Br J Surg* 1989, **76**. 99–100) advocating partial fundoplication after abdominal Heller's myotomy is critical of previous published work and in particular of a recent collective review[1] which concluded that a higher incidence of reflux is encountered after myotomy performed through the abdomen as opposed to the thoracic procedure. The data accrued from retrospective series on the short thoracic myotomy which does not extend beyond 1 cm into the stomach and which takes care to avoid disruption of the gastro-oesophageal fixation would support the view that this procedure is followed by an incidence of reflux which is half that following abdominal myotomy. This argument and the persistent controversy are circuitous since the data on which they are based are totally uncontrolled.

There is an ongoing study on achalasia in this department. To date, 18 patients have been studied by 24-h pH monitoring, manometry and oesophageal isotope transit before and after myotomy. Insofar as the reflux status is concerned, three patients demonstrated pathological acid reflux before myotomy and 15 did not. The latter group were treated by a short thoracic myotomy, and postoperative testing at 3–6 months showed no reflux. Thus it would seem that some patients have reflux preoperatively and would need an anti-reflux procedure whether the myotomy is carried out through the chest or the abdomen. The majority, one suspects, do not require this added procedure if the myotomy is performed through the chest. Perhaps more widespread preoperative testing for reflux would solve the controversy and allow rational patient selection. In the absence of hard evidence, one could postulate that the abdominal operation is more likely to disrupt gastro-oesophageal fixation and precipitate reflux. If an anti-reflux operation is considered advisable, it is indeed sensible to advocate an incomplete wrap since this is less likely to cause oesophageal emptying problems in view of the aperistaltic characteristic of this disorder.

Finally, in the interest of accuracy, Messrs Crookes *et al* should perhaps acknowledge that the operation they describe was reported several years ago by Toupet[2] and subsequently popularized by Boutelier and Jonsell[3]. For my part, I have found this operation superior to the complete wrap for the treatment of reflux disease and now use it routinely to treat this disorder.

A. Cuschieri

Ninewells Hospital and Medical School
Dundee DD1 9SY
UK

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Book reviews

A Colour Atlas of Surgical Management of Venous Disease

C V Ruckley. 308 × 254 mm. Pp 128. Illustrated. 1988. London Wolfe. £35.00

One of the perks of reviewing books is that you are usually rewarded by being allowed to keep the book Sometimes this is a dubious pleasure, but I am delighted to be able to place this highly illustrated and beautifully produced monograph on my shelves. Having recently produced a venous textbook, I am extremely envious of the superb colour operative pictures that Vaughan Ruckley and Wolfe Medical have used to illustrate this atlas. The book is primarily an operative manual, although it does contain sections on venous anatomy, assessment, sclerotherapy and compression therapy There are one or two technical points with which I would disagree, particularly the suggestion that the long saphenous vein should be divided before the saphenofemoral junction has been identified (even though the author stresses 'provided there is no doubt as to its identity') These apart, and all surgeons have their own operative idiosyncrasies, it is an excellent little book which should appeal to both the novice and the experienced surgeon alike I will encourage all our new Senior House Officers to read it before they start operating on patients with varicose veins and venous ulcers.

K. Burnand

Assistant Director
Surgical Unit
St. Thomas's Hospital
London SE1 7EH
UK

Microsurgery in Trauma

W. D Shaw and D A Hidalga. 216 × 279 mm Pp 396. Illustrated. 1987. New York, Futura Print Company $87 50.

Trauma is the leading cause of death among young adults, and is the commonest cause of permanent disability within the population The psychological, social and economic consequences of trauma demand the surgical skills of reconstruction and salvage to preserve function and appearance. Microsurgery has added a new dimension to this field, re-defining the rules of management, and encouraging early definitive and comprehensive reconstruction

This text is based on the experience of a single skilled plastic surgical department, well versed in the application of microsurgery in trauma The work is divided into four sections. the basic principles, replantation, nerve injuries and tissue transplantation

The first section contains useful information on the microscope and microinstruments, and provides a clear description of microsurgical techniques and methods for monitoring reconstructions

The section on replantation emphasizes the pathophysiological consequences of amputation and ischaemia. The mechanisms of injury are linked to defining the best possible goals, surgical management and subsequent outcome. Upper limb replantation is given more emphasis than lower, although the motivation to walk may be higher than to return to manual work, lower limb prostheses are well developed and well tolerated Secondary lower limb reconstructive procedures and salvage, however, have an important role

The section on nerve repair concentrates primarily on upper limb injuries Repair of avulsion of the roots of the brachial plexus is biologically and technically futile However, myelography is in itself not diagnostic of this condition and the authors consider that other diagnostic modalities, in particular surgical exploration, should also be undertaken

The largest section of the book is on tissue replantation Replantation techniques mean that the tissue available for reconstruction is not restricted to the local vicinity of an injury The wide variety of flaps, containing not only skin, but also muscles, tendons, vessels and nerves, provide unique characteristics appropriate to local needs The historical basis, surgical anatomy, flap design and flap dissection are considered for each donor site and a full bibliography supplied

The whole text provides a clearly written comprehensive cover of the chosen topic Detailed anatomy and practical procedures are discussed at a level that is not collectively available elsewhere The diagrams reflect the dual artistic and surgical background of the second author, and represent a unique guide to reconstructive procedures. The black-and-white photographs are not of equivalent quality, but do not detract from the overall value of the work

Management of these problems requires a skilled and well-organized team, with senior continuity Enough team members are required to ensure expert emergency and subsequent management, the optimal choice and undertaking of reconstructive procedures, and comprehensive postoperative care, rehabilitation and follow-up. The authors have succeeded in providing an excellent guide to these contemporary requirements for microsurgical reconstruction in trauma

J. S. P. Lumley

Professor of Surgery
St Bartholomew's Hospital
London EC1A 7BE
UK

Reducing Traffic Injury—A Global Challenge

G W. Trinca, I R. Johnston, B. J Campbell et al. *178 × 254 mm. Pp 112 1988. Melbourne A. H. Massina £13 00*

This short monograph is powerful stuff! It should be compulsory reading for those in the higher echelons of government and the medical and legal professions It has been written by seven individuals from Australia, Canada, the UK and the USA, all of whom have interest and expertise in road traffic injuries. They have come together under the umbrella of the National Road Trauma Committee of the Australasian College of Surgeons The Australasian College already has a fine record in the field of prevention of injury, having been largely responsible for the production of evidence about the efficacy of seat belts. It is good to see them continuing to forge ahead in this field Under the Chairmanship of Dr G. W Trinca, a Melbourne General Surgeon with a major interest in the prevention and management of road traffic injury, the authors have produced a compelling statement of the current and forthcoming problems and possible solutions.

The message is stark but simple In the world today, 15 million people are injured each year in road traffic accidents and half a million die By the turn of the century these numbers will double.

The seven chapters in this book cover the present situation, and they provide a forecast of the problems posed by rapidly increasing traffic throughout the world, a view of the role of institutions in dealing with the problems and a chapter on strategies to reduce injury One can tell this book has been written under the supervision of a surgeon The style is terse and hard-hitting Words are not wasted The problems are clearly stated and the recommendations are set out in short statements to give maximum impact

Much of what is written is directed at governments and major institutions such as the World Health Organization, the Organization for Economic Co-operation and Development and the World Bank However, there is advice for those whose task it is to manage the injured It is noteworthy, in view of the present debate taking place in this country, that the authors come down firmly in favour of an integrated trauma service with trauma centres for the treatment of the most severely injured

This book helps to restore the balance in terms of priorities in medical matters Perhaps cancer and heart disease, primarily conditions of the old and retired, have held the foreground for too long. It is time that injury, the principal cause of death in the young and economically active section of the community, was placed first on the agenda

This book will help to do this. It is mandatory reading for all interested in the prevention, as well as the management, of surgical disease

M. Irving

Chief Consultant Surgeon
Hope Hospital
Salford M6 8HD
UK

Notices and announcements

6–9 June 1990
Fourth International Conference on Malignant Lymphoma
Lugano, Switzerland
Information. Dr F Cavalli, Head of Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

12–13 June 1989
Cholelithorama: Total Gallstone Management
London, UK
Information. BDI Conferences Ltd., 3 Beaconsfield Terrace Road, London W14 0PP, UK

19–21 June 1989
Tripartite Meeting
Birmingham, UK
Information: Mr Roger Grace, The Royal Hospital, Wolverhampton, UK

21–23 June 1989
71st Annual Meeting of The Endocrine Society
Seattle, Washington, USA
Information. The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

6–7 July 1989
70th Meeting of the Surgical Research Society
Newcastle upon Tyne, UK
Information. Mr Alan J. Rich, Department of Surgery, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne, UK

13–15 July 1989
XIVth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

21–24 August 1989
4th International Symposium on Obesity Surgery
London, UK
Information: Mr E. R. T. C Owen, Academic Surgical Unit, The Queen Elizabeth Queen Mother Wing, St Mary's Hospital, Praed Street, London W2 1NY, UK

27 August–1 September 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Informtion. International Congress and Convention Association, PO Box 50006, Tel Aviv 61500, Israel

6–8 September 1989
Fourth World Congress of the International Society for Diseases of the Oesophagus
Chicago, Illinois, USA
Information: 4th World Congress of the International Society of Diseases of the Oesophagus, 911 Busse Highway, Park Ridge, Illinois 60068, USA

10–15 September 1989
3rd International Symposium on Inflammatory Bowel Diseases Jerusalem, Israel
Information International Congress and Convention Association, P.O. Box 5006, Tel Aviv 61500, Israel

10–15 September 1989
XIV World Congress of Otorhinolaryngology Head and Neck Surgery
Madrid, Spain
Information. Technical Exhibit Manager, XIV World Congress of Otorhinolaryngology, C/ Velazquez, 90-5th floor, 28006 Madrid, Spain

11–16 September 1989
33rd World Congress of Surgery
Toronto, Canada
Information 33rd World Congress of Surgery, Congress Canada, Congress Management, 73 Richmond Street West, Suite 300, Toronto, Canada M5H 1Z4

12 September 1989
10th Annual Study Day: the Role of the Plain Abdominal X-ray
Canterbury, UK
Information Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent and Canterbury Hospital, Canterbury, Kent CT1 3NG, UK

17–20 September 1989
The Centenary Congress of the Polish Surgical Association
Kraków, Poland
Information: Organizing Committee, ul Kopernika 40, 31-501 Kraków, Poland

17–26 September 1989
Frontiers in Gastroenterology: Colorectal Disease
Birmingham, UK
Information: Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

19–20 September 1989
New Trends in Pelvic Pouch Procedures
Bologna, Italy
Information R M. Società di Congressi srl, Via Ciro Menotti 11–20129, Milano, Italy

21–23 September 1989
Annual General Meeting of the Association of Surgeons in Training
Cardiff, Wales, UK
Information Mr B. Taylor, Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

22–24 September 1989
Association of Colon and Rectal Surgeons of India
Soura Sringar, India
Information: Dr N A Wani, Organizing Secretary, Room No 1318, Sher-i-Kashmir Institute of Medical Sciences, Soura Srinagar, India

27 September–1 October 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Information. The Secretariat, 2nd International Conference on Gastrointestinal Cancer, P O Box 50006, Tel Aviv 61500, Israel

29 September 1989
Progress in Microsurgical Training, Research and Clinical Support. The Sixth Annual Meeting of the Society of Microsurgical Specialists
Buffalo, New York, USA
Information. Elaine Lavigne, University of Vermont, Microsurgical Laboratory, Give Building E-302, Burlington, Vermont 05405, Massachusetts, USA

15–21 October 1989
Recent Advances in Pancreaticobiliary Surgery
Edinburgh, UK
Information. Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

16–20 October 1989
Sixth World Congress on Medical Informatics MEDINFO 89
Beijing, China
Information: Dr Phil R Manning, Chairman, Scientific Programme Committee, MEDINFO 89, USC School of Medicine, 1975 Zonal Avenue, KAM 317, Los Angeles, California 90033, USA

2–3 November 1989
International Soft Tissue Sarcoma Conference
London, UK
Information: Miss J. Mountsteven, Conference Centre, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

10–11 November 1989
4th Steglitz Pediatric Surgical Symposium Berlin Laser application in Children
Berlin, FRG
Information Priv Dos Dr Felix Schier, Department of Pediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, FRG

15–17 November 1989
Fourth EORTC Symposium on Advances in Gastrointestinal cancer: Research and Treatment
Strasbourg, France
Information: J. P Arnaud MD CMCO, 19 rue Louis Pasteur, Schiltigheim BP 120, 67042 Strasbourg Cedex, France

23–24 November 1989
Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland
Dundee, UK
Information: Mr James Forrester, Department of Surgery, Ninewells Hospital, Dundee DD1 9SY, UK

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr Joseph W. C. Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

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SPECIALTY EXAMINATION IN UROLOGY

Royal College of Surgeons of Edinburgh
Royal College of Surgeons of England
Royal College of Physicians and Surgeons of Glasgow
Royal College of Surgeons in Ireland

The next Intercollegiate Specialty Examination in Urology will be held in the London Hospital, Whitechapel, London, on Friday, 22 September 1989.

Candidates will be required to hold the Surgical Fellowship of one of the Royal Colleges of Surgeons of Great Britain or Ireland and to have completed a period of post-Fellowship training in posts approved by the Intercollegiate Board in Urology of not less than four years, as follows:

(a) one year in General Surgery in posts approved by the Joint Committee on Higher Surgical Training;
(b) three years in Clinical Urology in posts approved by the Specialist Advisory Committee in Urology. At least one year of this period must be at the Senior Registrar level.

The Regulations and application form may be obtained from the Secretariat, Intercollegiate Specialty Boards, 10 Hill Square, Edinburgh EH8 9DR.

Completed applications for entry must be received by Friday, 4 August 1989.

Fee: £230

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3-8 June 1990
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John Cameron – Cholangiocarcinoma
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Miles Little – HPB Trauma
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Michael Trede – Carcinoma of the Pancreas

Further information may be obtained from:

Miss Caroline Roney
HPB Congress Secretariat
65 West Drive, Sutton, Surrey SM2 7NB
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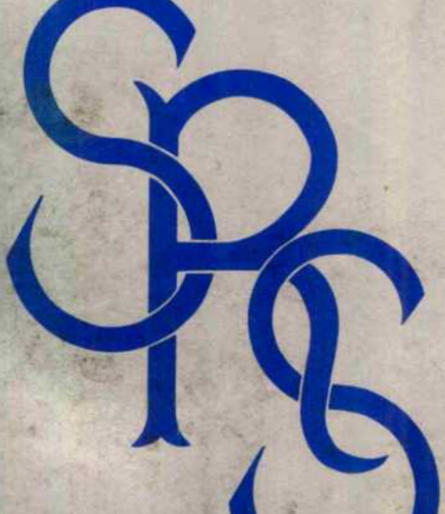

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All queries regarding submitted papers not yet accepted for publication should be addressed to Lynne Ponjee, Editorial Secretary, Butterworth Scientific Limited, PO Box 63, Westbury House, Bury Street, Guildford GU2 5BH, UK. Telephone: 0483 301439. Telegrams and Telex 859556 SCITEC G. Facsimile: 0483 301563.

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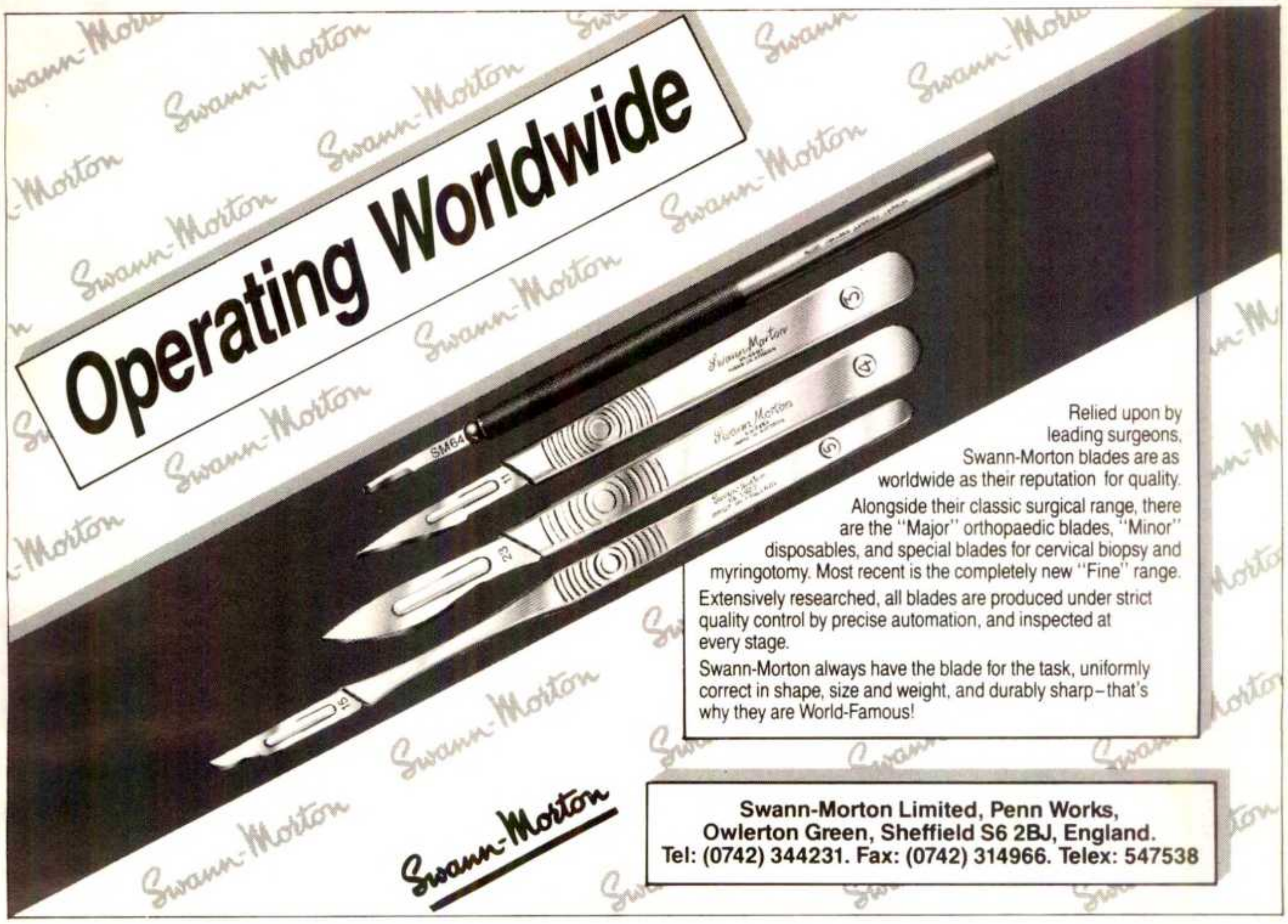

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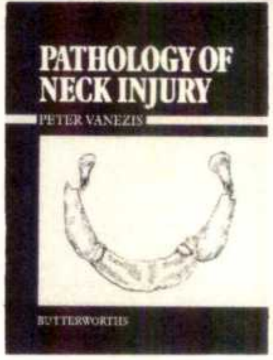

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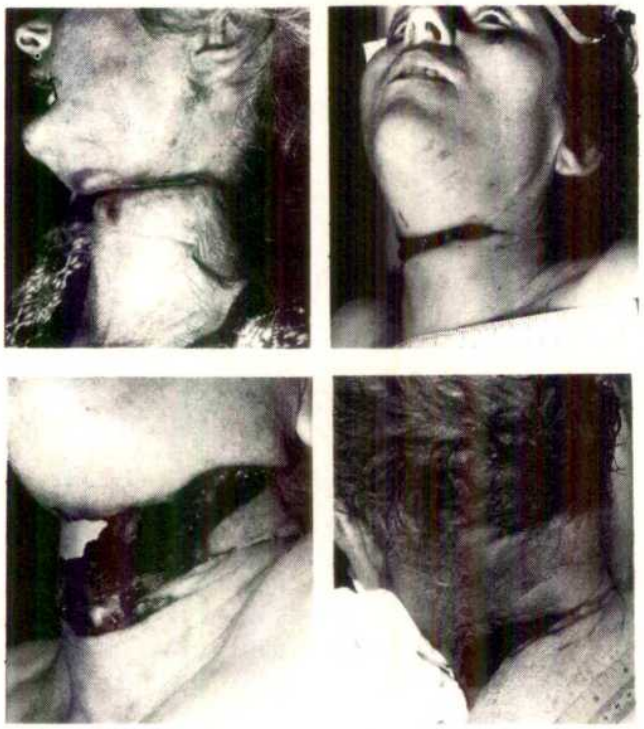

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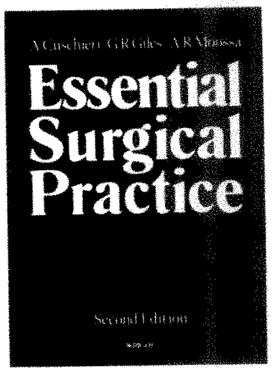

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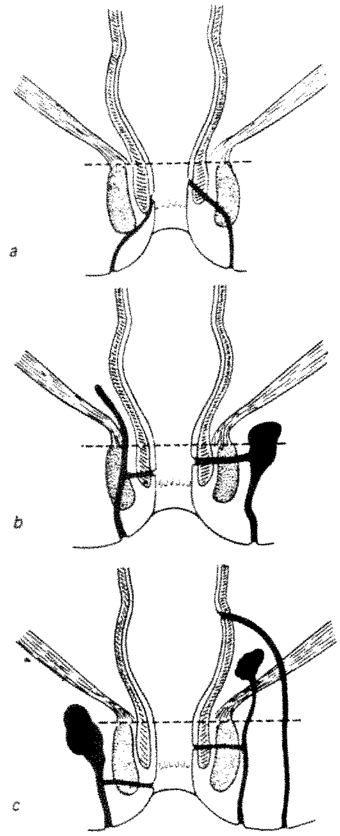

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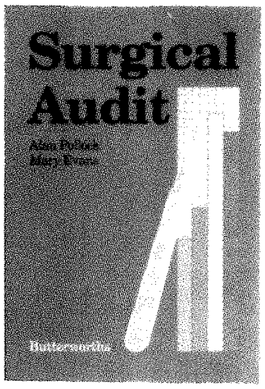

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Extending surgical audit: the assessment of postoperative outcome

Everyone involved in health care is subjected increasingly to greater accountability. The present Government's concept of 'value for money' seems destined to be applied more and more to the Health Service; a policy that will inevitably involve auditing not only resources but results. If surgeons are to 'sell' their skills on an internal National Health Service market, what criteria will be used to judge which hospital or firm or consultant is best for a particular referral? In many instances personality or geographical proximity will remain the major determinants. In other cases general practitioners and their patients may be guided more by proven results. Surgical audit seems destined to increase.

Auditing of process is already with us in the form of performance indicators of workload such as numbers of new out-patients, admissions and operations, and these are now applied to most surgeons in the UK. Yet the present emphasis on resources and their management has diverted attention from the aspect of more concern to doctors and patients – the outcome of surgical treatment. There is little merit in a clinician topping a league table for operations performed if these are inappropriate or the results are bad.

The case for surgical audit is now well established. Audit has advantages across the spectrum of those involved in patient care. It can tell surgeons how their results compare with those of their peers – an important contributor to job satisfaction perhaps, or a stimulus to improved technique. It can tell both surgeons and managers whether better performance indicators and lower costs are achieved at the expense of, for example, increased re-admission and complication rates. In short it can tell us all whether we are achieving our aims in surgical care.

Surgeons, especially gastrointestinal surgeons, were pioneers of auditing long-term outcome in their patients. Billroth was not only the father of gastrointestinal surgery but was the originator of surgical audit. In the UK, Tanner[1] and Visick[2] demonstrated both the feasibility and the value of long-term follow-up after peptic ulcer operations. These and a few others like them established exhaustive and detailed follow-up after gastric surgery and with them began reliable follow-up where only clinical impression had gone before. For example, in 1928 the largest prospective study then published, involving some 744 patients, reckoned the recurrent ulcer rate after gastroenterostomy at 2·8 per cent[3]. Even centres of excellence were not immune from dubious results; the recurrence rate at the Mayo Clinic was claimed to be 3·5 per cent after a minimum follow-up of 5 years[4]. These results we now know reflect inadequacy of follow-up rather than operative success. Has the audit of surgical outcome improved 60 years on?

Individual surgeons do not have the resources to follow up all cases in the long term. It is difficult enough for most surgeons to follow up those groups of patients in whom they have a particular interest. Pressure on hospital resources has squeezed out-patient clinics, making increasingly inappropriate the continued review of patients who remain well years after long-forgotten operations. How, then, can individual surgeons know whether their results compare with those published in the literature? How can individual surgeons know, for example: whether their recurrence rate after surgery for duodenal ulcer is 5 per cent or 40 per cent; whether their 5-year survival rate after resection for colorectal cancer is 40 per cent or 70 per cent; what the symptomatic results of their transurethral resections are after more than 1 year (how many of their patients are incontinent and how many require a further resection); whether their palliative resections for gastric cancer improve the quality of life or whether the patient is better off without surgery? It is unlikely that these questions can be answered by follow-up at the routine out-patient clinic without a structured document for collecting the data. Most surgical clinics are too busy to allow this additional time-consuming chore. It is equally unlikely that surgeons would take time to analyse such documents manually. If an audit system is to succeed it must involve minimal extra work for clinicians and secretarial or clerical staff; it must be cheap and easy to use; and it must provide relevant results which are wanted by the clinician.

The origins and working of our Surgical Review Office formed a logical, natural progression from a gastric follow-up clinic. The decline in incidence of peptic ulcer since the 1960s and the even more dramatic decline in its surgery in the 1980s necessitated diversification into other areas. Our system now audits operations for peptic ulcer (elective and emergency), gastric cancer, gastro-oesophageal reflux and colorectal cancer. The detailed techniques of recruitment, documentation and follow-up have been described elsewhere[5].

Who should do the audit? Registrars and research fellows are employed on a short-term basis. As a result, short-term follow-up studies abound, as do 'snapshot' studies of the last 50 '-ectomies' or '-plasties'. But to obtain a sustained long-term audit of a consultant's results requires that the consultant should make time to do it personally. Only the consultant has the

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continuity of employment to sustain the continuing organization of a long-term audit system.

Whilst enthusiasts have and will continue to audit their results for self-assessment, others remain to be convinced. There are some who believe that if our political and managerial masters wish to know the results of our clinical endeavours it is they and not we who should do the auditing. This option, which would involve employing medically qualified 'assessors' working for the manager, is an option that would be much less attractive to most clinicians and unacceptable to many.

Deciding which groups of patients to study in a consultant's or firm's practice and what information to collect about them involves little time and no financial outlay. The powerful commercial database packages now widely available for modern microcomputers make design of the collecting documents easy – the days of elaborate codes and margins full of numbered boxes are over. The proforma should record biographical, clinical and follow-up data. Follow-up will be increasingly carried out by postal questionnaire worded in a form that all patients can understand. The answers should be capable of direct entry on to a computer without any data manipulation or analysis.

The choice of a computer system assumes little computer knowledge and less enthusiasm, although this is progressively changing as consultants are appointed from a computer-literate generation. The system should be on the list approved by the Health Authority, should be able to run a 'friendly' commercial database, and should have at least 20 megabytes of hard disk storage. Computer costs are falling and will continue to fall.

Having said this, the decision about who should pay for the exercise should be clarified from the outset. Enthusiasts like Visick established follow-up systems out of their own pockets, but today most are financed by 'soft' money. As has happened in Lothian, UK, consultant commitment to audit can result in the Health Authority subsequently funding the system[6]. Few managers are likely, even in the current climate, to view this as a priority. Consultant commitment to the principle and a system bought with soft money will continue to be the most common method of starting up.

If auditing of outcome is to become widely established, however, it must have the support of the Royal Colleges. If they are to retain their role as guardians of quality control of a self-regulating profession they should ensure that only those units that practice audit are recognized as training posts. The Government, as paymaster of the National Health Service, has a vested interest in establishing formal quality control. The recommendations of the National Audit Office report *Quality of care in the NHS*[7] seem likely to be implemented.

Surgical audit is here to stay and destined to increase. The enumeration of patients seen and operations performed is a prerequisite in assessing performance of a surgical firm. Such statistics enable the rational planning of medical manpower and funds. Basic audit within a firm must be a criterion for recognition of surgical posts for training. Yet they only show one side of the coin – the quantity of workload but not the quality of care. Meaningful audit must include the assessment of outcome. This means prospective and long-term follow-up, which should be as complete as possible.

A postal questionnaire is more convenient and less time consuming for patient and surgeon and is cheaper for the National Health Service. Follow-up must also be long term. The early results of highly selective vagotomy claimed a recurrence rate of about 1 per cent after 2–3 years[8]. After 14–19 years the recurrence rate on the same patients was 30 per cent[9].

The audit of outcome therefore must be prospective, structured, long term and computer based. It is easy to establish. Its continued success requires from surgeons a commitment to the quality control of their work and from managers a modest resource allocation.

I. M. C. Macintyre

Surgical Review Office
Western General Hospital
Edinburgh EH4 2XU
UK

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Pancreatic cysts and pseudocysts: new rules for a new game

Not many years ago the management of pancreatic pseudocysts was thought to be relatively simple, the major controversy being whether to intervene surgically immediately for external drainage or to wait until maturation for internal drainage. The issues have become more complex, and more interesting, with the development of ultrasound and computed tomographic (CT) scanning, endoscopic pancreatography and percutaneous and endoscopic sampling and drainage techniques. These technological advances have highlighted the differences between acute and chronic pseudocysts, have shown that some pseudocysts can resolve spontaneously, have helped to discriminate which are infected or likely to persist, have provided an alternative to surgical treatment in some cases, and have brought to attention that other cystic lesions of the pancreas, particularly cystic neoplasms, are more common than previously appreciated and must be recognized and treated differently from pseudocysts.

This last issue is perhaps the first to be considered. Half of the cystic neoplasms we treated during one period had been referred after another surgeon had already erroneously created a cyst–enteric anastomosis on the presumption he was draining a pseudocyst[1]. While microcystic tumours are usually benign, macrocystic tumours are probably all malignant or at least premalignant. These include cystadenocarcinomas, papillary cystic neoplasms and cystic islet cell tumours. None the less, they are usually slow growing and the majority are curable by surgical resection, large size notwithstanding. Cystic neoplasms occur more often in women, mainly of middle age. There is often a history of abdominal pain, but more and more are being found by serendipity in asymptomatic patients having ultrasound or CT scans for irrelevant reasons. These lesions are frequently large (average, 10 cm). They may be single or multilocular and can frequently be shown to be irregular or septated, or contain a solid component. The cyst wall may be calcified. The amylase content of the serum (and cyst contents) is within normal limits, in contrast to the raised levels noted in half of the sera and all of the cyst fluids of pseudocyst patients. Pancreatography characteristically shows no communication between the duct and the lumen of neoplastic cysts, whereas a communication can be demonstrated with at least two-thirds of pseudocysts. Cystic tumours, despite their probable slow progression and long natural history, should be resected in any patient fit for the operation. The diagnosis can be confirmed by cyst wall biopsy, which can be expected to show an epithelial lining. Finding this in a patient being operated on to drain a 'pseudocyst' should alter the diagnosis and the surgical strategy. Simple (non-neoplastic) cysts need no treatment, but enterogenous cysts, which occur in the head of the gland, may require resection because they can be the cause rather than the product of pancreatitis.

Pseudocysts by definition do not have an epithelial lining. They are fluid collections, usually rich in pancreatic secretions, which have escaped from a duct system disrupted by acute inflammation or obstructed by stricture or stone. The peripancreatic fluid collections commonly seen by ultrasound or CT early in acute pancreatitis are not really pseudocysts, and generally are reabsorbed without complication and without the need to be evacuated. Persistence and encapsulation occur in perhaps 5 per cent. Conversely, early pancreatic swelling (phlegmon) may develop regions of pancreatic and peripancreatic necrosis, which in turn may partially liquefy and evolve into a pseudocyst[2]. CT scanning has become invaluable for monitoring the course of these events.

Several studies have illustrated that pseudocysts occurring after acute pancreatitis behave differently from those found in chronic pancreatitis[3,4]. The former represent a complication of pancreatic necrosis, tend to occur in sicker, more unstable, patients, are more likely to become complicated by infection, haemorrhage or rupture and are less likely to have a wall thickness adequate to hold sutures for internal drainage. Paradoxically, acute pseudocysts are more likely to resolve without interventional drainage[4], but in perspective only 15 per cent of true acute pseudocysts, as distinct from acute peripancreatic fluid collections, healed spontaneously in our experience[3]. It is not known whether percutaneous catheter drainage of early acute pseudocysts will facilitate or speed healing, but the need to remove associated necrotic remains of the destructive process may ultimately determine that an operation must be performed anyway[5]. Patients who are clinically stable can be watched, but continuing signs of toxicity or suspicion of infection should mandate intervention. Percutaneous aspiration of the cyst has been proved to be accurate and safe in detecting infection when the clinical signs are equivocal[6] and catheter drainage can be used as treatment in this circumstance[7]. In general, the strategy for acute pseudocysts is to wait while the patient's condition permits and to wait no longer if he deteriorates.

Pseudocysts in chronic pancreatitis most often are found in the absence of a recent attack of acute pancreatitis. These patients are rarely acutely ill, nor do they often encounter the acute complications so much more common in acute pseudocysts. Pseudocysts of chronic pathogenesis usually have a mature capsule already present at discovery and rarely regress, perhaps never,

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if over 6 cm in diameter. Drainage is indicated in symptomatic patients and can be carried out immediately[3,4]. The natural history of small chronic pseudocysts in asymptomatic patients is not well defined, but it appears safe to observe them. Preoperative endoscopic pancreatography may have a role in the evaluation of chronic pseudocysts to ascertain associated intrapancreatic biliary stenosis as well as pancreatic duct dilation and obstruction[8]. The finding of these associated conditions may indicate the desirability of draining the bile duct and/or pancreatic duct when the pseudocyst is operated on, and indeed may bias the choice of treatment toward surgery and predicate the type of drainage procedure (i.e. resection of the pancreatic tail or cystjejunostomy plus pancreatojejunostomy, instead of cystgastrostomy).

The treatment of mature pancreatic pseudocysts can now be accomplished by various means, surgical and non-surgical. The surgeon can create an anastomosis to the stomach, duodenum, or to a Roux-en-Y loop of jejunum. The choice seems best determined by the size and location of the pseudocyst: large adherent retrogastric cysts are conveniently drained into the stomach; cysts within the duodenal sweep are often most easily drained into the duodenum; the jejunum must be brought to cysts in the pancreatic tail or those presenting inferiorly through the mesocolon, perhaps from the uncinate process. Distal pseudocysts can be resected with the pancreatic tail, and this may be preferred when the spleen is involved or there has been intracystic haemorrhage. Complication and late recurrence rates should both be low, in the order of 5 per cent or less[3,4].

However, both interventional radiologists and endoscopists have challenged the surgeon's traditional prerogative for drainage. While therapeutic needle aspiration has a high recurrence rate (about 75 per cent), prolonged percutaneous catheter drainage has had reported success rates of 70–100 per cent in small series[9,10]. Introduction of clinically important infection has been more feared than found. Occasional persistent fistulae or recurrence after percutaneous catheter drainage attest to the fact that pancreatic duct obstruction may be the underlying predisposing cause of the original 'blow-out' and of the continuing complications. I speculate that endoscopic pancreatography could be usefully predictive here: if free communication between the pseudocyst and pancreatic duct can be proved, catheter drainage may be most likely to succeed. If, on the other hand, there is a blocked pancreatic duct, it may be supposed that the pseudocyst will require a permanent alternative pathway for internal drainage.

There is a small reported experience with drainage of pseudocyst using the endoscope. It has been shown that endoscopical electrocautery can be used to cut into a pseudocyst that bulges into the gastric or duodenal lumen[11]. Stent catheters can also be placed through the wall to achieve limited internal drainage. What cannot be evaluated yet is the relative risk and efficacy of these techniques. Massive bleeding from the gut wall or a pancreatic vessel is a theoretical threat which has been realized on occasion. Non-adherence between the cyst and the adjacent gastric wall, resulting in free perforation into the peritoneal cavity, is another fearful possibility, not yet seen or perhaps just not yet reported. None the less, speaking as one who with singular lack of perspicacity once wrongly predicted that rampant disaster would result from percutaneous needle biopsy of the pancreas, I will this time take a more circumspect wait-and-see position.

The new options not only facilitate precise diagnosis but also underline its importance. The differentiation between acute and chronic pseudocysts, presence or absence of infection and necrotic debris, and associated abnormalities of pancreatic and biliary ducts all should modify the approach to treatment Even more critical, if a non-surgical treatment option is to be used, one must be certain that the lesion is a pseudocyst and not a neoplasm masquerading as one.

Harvard Medical School
Massachusetts General Hospital
Boston, USA

A. L. Warshaw

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Gastric cancer: a 25-year review

W. H. Allum,
D. J. Powell*,
C. C. McConkey* and
J. W. L. Fielding

Department of Surgery and
**Birmingham Regional Cancer Registry, Queen Elizabeth Hospital, Birmingham, UK*
Correspondence to:
Mr W. H. Allum, Department of Surgery, Clinical Sciences Building,
Leicester Royal Infirmary,
Leicester LE2 7LX, UK

Between 1957 and 1981, 31 716 cases of gastric cancer were registered in the West Midlands, UK. The age-standardized incidence has shown a decrease from 17·42 per 100 000 population during the first quinquennium to 15·30 per 100 000 in the last. There was an apparent increase in the proportion of proximal lesions with a decrease in the proportion of distal, antral cancers. The stage of disease at diagnosis remained constant with 79 per cent of patients having stage IV disease. Less than 1 per cent presented with stage I disease. As a result, the curative resection rate was 21 per cent. The operative mortality rates for curative partial gastrectomy and total gastrectomy were 13 and 29 per cent respectively. Surgeons undertaking more than nine total gastrectomies annually had an overall mean operative mortality rate of 22 per cent. Overall age-adjusted survival at 5 years was 5 per cent. Survival at 5 years for stage I, II and III disease was 72, 32 and 10 per cent respectively. There was a significant increase in survival time for those treated by curative resection between 1972 and 1981 compared with the previous decade. The implications for the management of gastric cancer are discussed.

Keywords: Gastric cancer, overall incidence, treatment and survival, operative mortality, resection

In 1965 a report from the Birmingham Regional Cancer Registry described the presentation, management and treatment results of patients with gastric cancer diagnosed in the West Midlands region, UK between 1950 and 1959. The overall 5-year survival rate was 4·9 per cent and this had not changed when compared with the preceding 15-year period[1]. This study was initially hospital based but became population based after 1957. Since the time of this report a number of factors have evolved which have had important implications for the treatment of gastric cancer. These include the availability of routine double contrast radiological studies and flexible fibreoptic endoscopy. In addition, improvements in anaesthetic management and in surgical techniques have been widely practised. Finally, experience from Japan has demonstrated that the adoption of recommendations[2] for careful surgical assessment and histopathological evaluation for all stages of gastric cancer can produce far better results than have been reported in the West[3].

With the background of these factors we now report the results of management of gastric cancer for the 25-year period from 1957 to 1981. During this period the Cancer Registry was wholly population based and over 95 per cent of all cases occurring in the region were registered[4]. Particular emphasis has been placed on the incidence of disease, the methods of treatment, the operative mortality for those undergoing resection and the end results of treatment.

Patients and methods

All patients registered at the Birmingham Cancer Registry with a clinical or histological diagnosis of stomach cancer between 1957 and 1981 have been reviewed Data already recorded by the Registry from patient notes include clinical features, diagnostic methods, treatment, histological findings and survival. All patients have been staged if necessary by reviewing the notes according to a clinicopathological system which takes into account histologically proven and unproven tumours (*Table 1*)[5]. In those patients not undergoing surgery, the reasons for withholding treatment have been evaluated.

Patients have been followed for a minimum of 5 years and survival has been expressed as age-adjusted survival rates This adjustment has been made in order to allow for the increasing mortality from all causes with increasing age[6]. As survival rates are particularly sensitive to the age range of the patients, and may appear unduly low when many are elderly, it is now common practice to use an age-adjusted or 'relative' survival rate, making allowance for the increase in 'natural mortality' by means of the Life Table[7] Forty patients (0·1 per cent) could not be traced to 5 years. In accordance with our usual practice these have been counted as dead at the time of the last known review. Statistical analysis was by the Student's *t* test.

Results

Incidence

During the period 1957–81, 31 716 cases of gastric cancer were registered. The population of the West Midlands has increased by 7·2 per cent during the study period[8]. However, using the 1971 population census figure of 5·11 × 10⁶ as the denominator for the whole period, this gives a crude annual incidence of 24·7 per 100 000. The incidence for each quinquennium is shown in *Table 2* The age-standardized rates clearly demonstrate a decrease in incidence following an initial rise over the first quinquennium. This rise probably reflects the improvement in data collection which occurred up to 1960. Since that time the efficiency of registration is believed to be over 95 per cent[4] The 31 716 cases included 149 cases of sarcoma, carcinoid or mixed tumours. In view of the different patterns of treatment and survival, these cases have been excluded from all subsequent analyses, leaving 31 567 for review.

The sites of disease were specified for 17 246 (54·6 per cent) cases. The remaining 14 321 (45·4 per cent) cases were either

Table 1 *Staging system for gastric carcinoma*

Stage	Clinical	Pathology
I	Radical resection	Muscularis propria – Serosa – Node – ($T_1N_0M_0$)
II	Radical resection ($T_{2\text{–}4}N_0M_0$)	Muscularis propria + Serosa ± Node – ($T_{2\text{–}4}N_0M_0$)
III	Radical resection ($T_{X\text{–}4}N_{1\text{–}3}M_0$)	Muscularis propria ± Serosa ± Node + ($T_{X\text{–}4}N_{1\text{–}3}M_0$)
IVa	Palliative resection ($T_{X\text{–}4}N_{X\text{–}3}M_{0\text{–}1}$)	Residual disease ($T_{X\text{–}4}N_{0\text{–}3}M_{0\text{–}1}$)
IVb	No resection ($T_{X\text{–}4}N_{X\text{–}3}M_{0\text{–}1}$)	Positive histology ($T_4N_{0\text{–}3}M_{0\text{–}1}$)

This Table has been reproduced from Fielding *et al.*[5]

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Table 2 *Incidence of gastric cancer for each 5-year period*

	Total cases	Average annual rates/100 000	
		Crude	Age standardization*
1957–61	5575	23·44	17·42
1962–66	6631	26·88	19·22
1967–71	6546	25·62	17·70
1972–76	6621	25·54	16·53
1977–81	6343	24·88	15·30

*Standardized to world population

Table 3 *Proportion of lesions by site for each 5-year period*

	Total specified	Site of lesion (%)			
		Cardia	Body	Antrum	Other single
1957–61	2490	11·3	17·5	45·9	25·3
1962–66	2866	11·6	18·9	45·5	24·0
1967–71	3376	16·7	17·6	39·6	26·1
1972–76	4155	17·5	22·0	35·3	25·2
1977–81	4359	21·2	19·5	33·0	26·3
Total	17246				

Table 4 *Distribution by stage for each 5-year period*

	Stage (%)					
	I	II	III	IVa	IVb	Curative treatment: stage not known
1957–61	0·5	5·1	11·0	6·4	72·4	4·6
1962–66	0·6	6·0	10·6	6·6	73·4	2·8
1967–71	0·5	5·7	10·8	9·2	71·1	2·7
1972–76	0·6	5·2	10·2	10·7	70·0	3·3
1977–81	0·9	5·8	13·7	8·9	66·7	4·0

unspecified or involved more than one site. The percentage of cases for which the site was specified increased from 44·8 per cent in 1957–61 to 69·1 per cent in 1977–81. The specified sites have been classified as the three principal anatomical areas of the stomach: cardia, body, and pyloric antrum. Lesions have been additionally classified into other single sites. The percentage of classified cases for each site occurring during each quinquennium is shown in *Table 3*. There is an apparent increase in the proportion of proximal lesions with a corresponding decrease in the proportion of distal, antral lesions.

The distribution of stage of disease is shown in *Table 4*. There has been very little change in the incidence of stage at presentation. There is a marginal increase in the numbers of lesions amenable to palliative resection (stage IVa), with a corresponding decrease in those receiving no treatment during the later years of the study.

Treatment

The types of treatment have been classified as curative, palliative, other or none. The curative group includes all who have had a resection with intent to cure and by definition had stage I–III disease. The palliative resection group were stage IVa and, again by definition, the remaining patients were stage IVb (*Table 5*). The laparotomy rate for the whole group was 55·6 per cent, with curative resection being undertaken in 6588 or 20·8 per cent of all patients. However, no treatment was carried out in 13 409 or 42·5 per cent of the whole group.

Operative mortality

Resection was undertaken in 9247 (29·3 per cent) patients; for cure in 6588 (20·8 per cent) and for palliation in 2659 (8·4 per cent). In the curative group, total gastrectomy was done in 1330 (20·2 per cent) and partial gastrectomy, including proximal and distal procedures, in 5258 (79·8 per cent). The operative mortality, defined as death within 30 days of operation, for these patients is shown in *Table 6*. For total gastrectomy the overall operative mortality was 28·8 per cent and for partial gastrectomy it was 13·0 per cent. For comparison, the operative mortality rates for palliative resections were 36·6 per cent for total gastrectomy and 23·0 per cent for partial gastrectomy. Furthermore, the 30-day mortality rate for those undergoing laparotomy alone was 35·8 per cent, contrasting with a rate of 49·0 per cent for those receiving no treatment.

These rates have been calculated for the whole study period. Analysis of the rates by quinquennium has demonstrated that there is no obvious improvement or deterioration in recent years.

In an attempt to determine factors influencing the outcome of surgery, the experience of surgeons has been evaluated. Experience has been evaluated for all gastrectomies, curative or palliative and total or partial. The number of curative gastrectomies performed annually by each surgeon has been calculated (*Table 7*). The median number of resections was 4·6 per year; thus 50 per cent of all resections were done by surgeons doing less than five procedures per year. For partial gastrectomy

Table 5 *Distribution by type of treatment*

Treatment	No. of cases	Distribution (%)
Curative resection		
Total gastrectomy	1330	4·2
Partial gastrectomy	5258	16·6
Palliative resection		
Total gastrectomy	478	1·5
Partial gastrectomy	2181	6·9
Other treatments		
Bypass	2328	7·4
Laparotomy and intubation	735	2·3
Laparotomy and adjuvant therapy	373	1·2
Laparotomy only	4882	15·5
No laparotomy		
Intubation	315	1·0
Chemotherapy or radiotherapy	278	0·9
Not treated	13409	42·5
Total	31567	

Table 6 *One-month mortality of resected cases by stage and treatment*

	No. of cases	Deaths
Stage I		
Total gastrectomy	17	3 (17·7)
Partial gastrectomy	176	11 (6·3)
Stage II		
Total gastrectomy	269	76 (28·3)
Partial gastrectomy	1485	176 (11·9)
Stage III		
Total gastrectomy	870	247 (28·4)
Partial gastrectomy	2682	357 (13·3)
Curative resection: stage not known		
Total gastrectomy	174	57 (32·8)
Partial gastrectomy	915	139 (15·2)
Stage IVa		
Total gastrectomy	478	175 (36·6)
Partial gastrectomy	2181	502 (23·0)

Values in parentheses are percentages

Table 7 *Number of resections per year and operative mortality*

Number of resections per year	Curative total gastrectomy			Curative partial gastrectomy		
	No. of consultants	No. of cases	Operative mortality (%)	No. of consultants	No. of cases	Operative mortality (%)
0–3	54	157	29·9	104	862	11·3
4–6	80	638	31·0	84	2603	13·4
7–9	20	346	26·6	20	1193	12·2
Over 9	5	134	21·6	5	421	13·3
Not known	—	55	30·9	—	179	19·6
Total	159	1330	29·0	213	5258	13·0

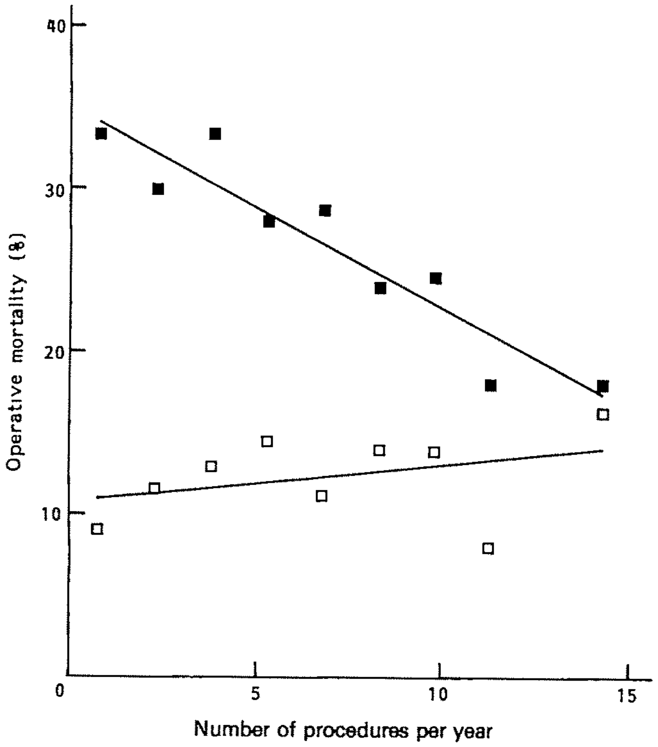

Figure 1 *Operative mortality for partial (□) and total (■) gastrectomy related to frequency of either procedure*

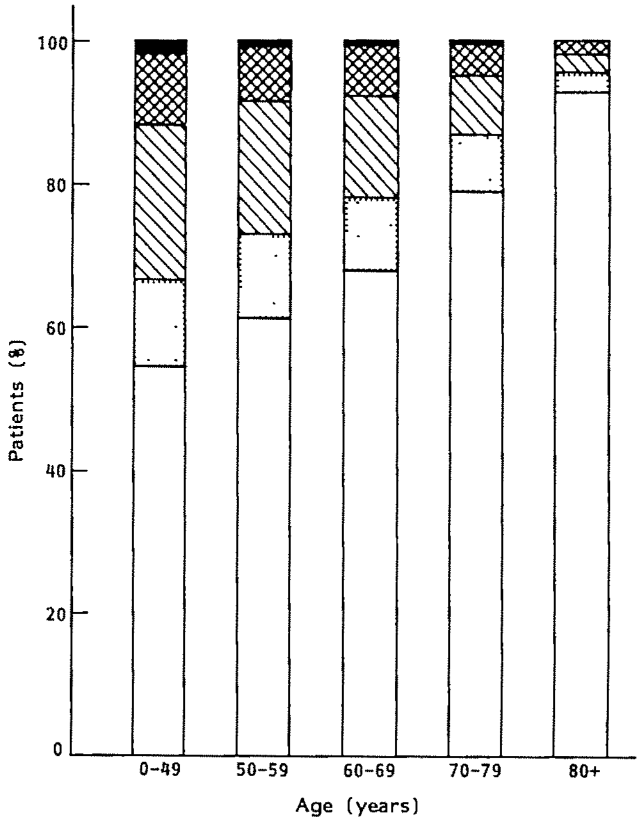

Figure 2 *Distribution of patients by stage and age.* ■, *Stage I;* ▩, *stage II;* ■, *stage III,* ⊡, *stage IVa,* □, *stage IVb*

Table 8 *Reasons for no curative treatment*

Reason	No. of cases
Too advanced	19 728
Poor general condition	2 498
Refusal	877
Found at autopsy	1 440
Other or not known	436
Total	24 979

the operative mortality rates were not influenced by the number of procedures performed, and approximated to the overall figure of 13 per cent (*Figure 1*). For total gastrectomy, however, the operative mortality declined with the increasing frequency of operation. Thus for those surgeons performing an average of more than nine resections per year the operative mortality rate was 21·6 per cent (134 resections) compared with 30·8 per cent (795 resections) for those performing six or less ($t=2{\cdot}16$ $P=0{\cdot}05$; *Figuere 1*).

Reasons for treatment

Factors influencing the selection of treatment are difficult to determine from a retrospective study such as this. However, data are recorded which demonstrate why curative treatment was not undertaken (*Table 8*). All patients included in this category had stage IV disease by definition of the clinicopathological staging system used in this study[5] as they had gross residual disease. To a certain extent, staging of these patients has been more dependent on clinical parameters alone as less than half had a laparotomy (*Table 5*).

The commonest contraindication to curative treatment was the extent of disease ($n = 19\,728$, 79·0 per cent) which included both locally advanced lesions and distant metastatic disease. Poor general condition, treatment refusal and diagnosis at autopsy accounted for most of the remainder ($n = 4815$, 19·3 per cent)

The effect of age has also been assessed for its part in treatment selection. As age increased the proportion of patients not undergoing curative treatment also increased (*Figure 2*). Although a decrease in the extent of disease and an increase in those in poor health appear to account for the effect of age on treatment (*Figure 3*), a direct relationship should not be inferred. In the analysis of the Registry records only one of the principal contraindications to curative treatment has been documented. Thus it is likely that many in poor health would also have had advanced disease, and the decrease in the extent of disease could be an apparent rather than true phenomenon.

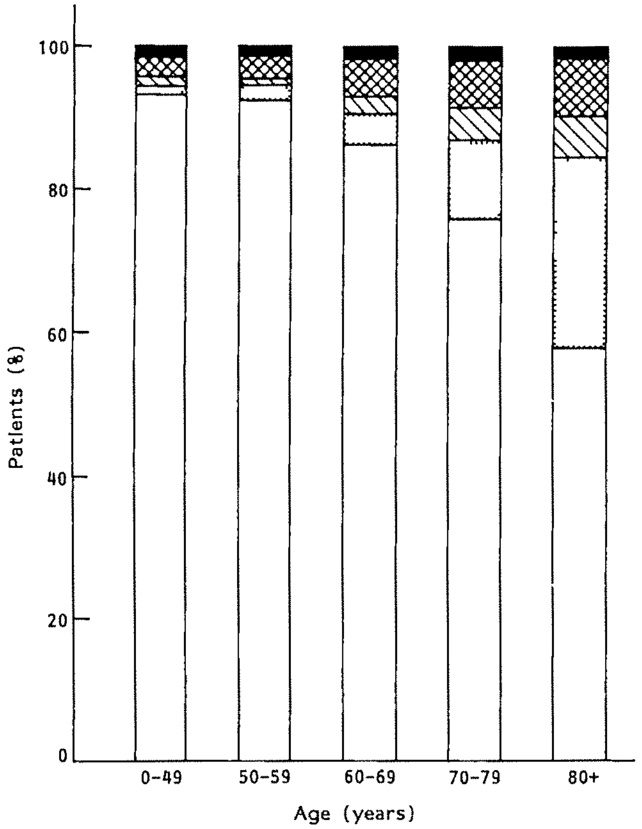

Figure 3 *Distribution by age of contraindications to treatment in stage IV disease* ■, *Other or not known*; ▩, *found at post mortem*, ■, *refusal*, ▧, *poor general condition*, ☐, *too advanced*

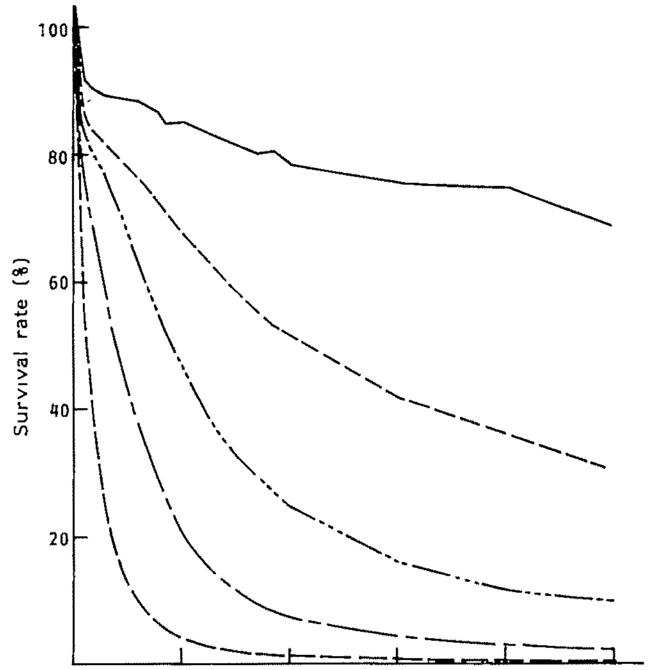

Figure 4 *Overall 5-year survival by stage of disease*. ——, *Stage I*, ---, *stage II*,-----, *stage III*, ---, *stage IVa*; ---, *stage IVb*

Survival

The overall 5-year survival was 4·5 per cent. Analysis of survival by quinquennium has shown an increasing trend from 3·8 per cent in 1957–61 to 5·2 per cent for 1977–81. Survival by stage is shown in *Figure 4*. Patients with lesions amenable to curative resection have 5-year survival rates of 72, 32 and 10 per cent for stages I, II and III respectively More distally situated lesions were associated with a better survival than were proximal tumours for antral lesions the survival rates were 75·8 per cent for stage I, 35·5 per cent for stage II and 11·8 per cent for stage III; for cardia survival rates were 23 3 per cent for stage II and 4·9 per cent for stage III. (The number of stage I tumours of the cardia ($n = 7$) was too few for assessment.)

Survival by treatment demonstrated an overall rate of 9·5 per cent for curative total gastrectomy and 22·7 per cent for curative partial gastrectomy. During the study period survival tended to improve for both procedures (*Table 9*). Although the differences in overall survival for both procedures did not reach statistical significance, this trend became significant for partial gastrectomy after exclusion of the operative deaths. Furthermore, when cases are stratified by stage, the results of curative resection (i e. combining both partial and total gastrectomy) show an improving survival trend. Again after exclusion of the operative deaths, both differences reach statistical significance at the 5 per cent level and if all curative resections are considered together, including those in which the stage is not known, the improvement in survival reaches significance at the 1 per cent level.

Analysis of survival by age for each of the stages demonstrates consistent rates for all ages (*Figure 5*), suggesting that the survival effect of age *per se* is minimal.

Since the majority of patients had advanced disease, the results of palliative treatment are of interest. For patients undergoing palliative resection, survival to 12 months was 21 per cent, falling to 7·4 per cent at 2 years. Overall, those with unresectable lesions had a 6 per cent chance of surviving 12 months, with those undergoing intubation faring worse than those having a laparotomy only. This probably reflects a higher proportion of proximal lesions in the intubation group, which, as has been shown, had a worse prognosis.

Discussion

The findings in this large series reflect the pattern of presentation and management of gastric cancer in one region in the UK. As with the previous report from this region[1], there is little in the literature to suggest that the overall approach to gastric cancer in the West Midlands differs from the rest of the UK. While it is fully recognized that this is a retrospective analysis and that important contributing factors to the full picture may be unavailable, its strength lies in the large numbers, the quality of the data and its population basis, all of which obviate the

Table 9 *Five-year survival following curative surgery for patients treated during 1962–71 and 1972–81*

	Survival (%)	
	1962–71	1972–81
Curative surgery		
Total gastrectomy	8 7	11·4 ($t = 1{\cdot}49$, n.s)
Partial gastrectomy	21 7	24 1 ($t = 1{\cdot}87$, n.s)
Excluding operative deaths		
Total gastrectomy	12·1	15 6 ($t = 1{\cdot}43$, n s)
Partial gastrectomy	24·5	28 1 ($t = 2{\cdot}5$, $P < 0{\cdot}05$)
Curative surgery		
Stages I and II	34·4	38 7 ($t = 1{\cdot}80$, n s.)
Stage III	8 9	10·7 ($t = 1{\cdot}64$, n.s.)
Stages I, II, III and not known	19 1	21 4 ($t = 2{\cdot}1$, $P < 0{\cdot}05$)
Excluding operative deaths		
Stages I and II	39·4	44 9 ($t = 2{\cdot}09$, $P < 0{\cdot}05$)
Stage III	10·5	13·2 ($t = 2{\cdot}06$, $P < 0{\cdot}05$)
Stages I, II, III and not known	22 4	25·8 ($t = 2{\cdot}68$, $P < 0{\cdot}01$)

n s , Not significant

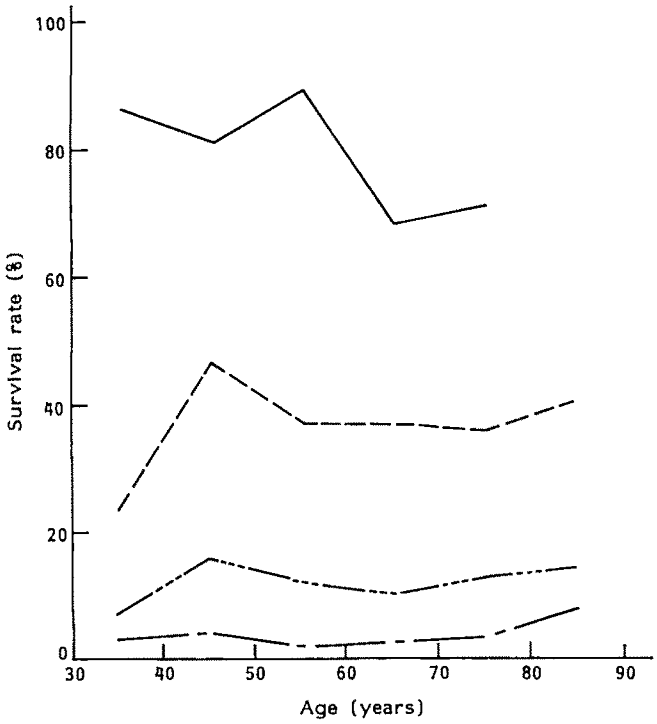

Figure 5 *Five-year survival by age for each stage of disease* ——, *Stage I*, ----, *stage II*; -----, *stage III*; ---, *stage IV*

possible bias present in even the largest hospital series. Hence a number of conclusions can be made that, in the context of the current trend towards the adoption of the Japanese approach to gastric cancer[3,9], are worthy of general discussion.

In both western Europe and the USA the incidence of gastric cancer has been decreasing[10]. In this study, despite the increasing age of the population during the period under review, the age-standardized incidence has shown a similar decrease. Analysis of the data also suggests an increase in the proportion of proximal lesions with a corresponding decrease in distal, antral tumours. These differences are currently being further evaluated. In series from the USA, a far greater increase in the proportion of proximal lesions has been reported[11]. This has been concurrent with an increase in the incidence of diffuse-type tumours. It may be that dietary changes with a reduction in stored and preserved foods have reduced the intake of harmful nitrates and hence the exposure of the distal stomach to carcinogens. As a result, the proportion of proximal lesions has increased relatively.

The most striking feature of this series is the constancy of the stage of disease at presentation. Throughout the study period, 80 per cent of patients have had disease considered to be too extensive for radical surgery. Similarly, the proportion of patients with stage I disease has remained constant at 0·7 per cent. Other reports have demonstrated a recent increase in the incidence of early lesions describing rates of 10–12 per cent[12,13]. Such increases have been attributed to the widespread use of upper gastrointestinal endoscopy. This has been similarly widely available in the West Midlands during the latter half of the study, yet without a corresponding increase in incidence Those studies reporting greater incidence originate from single centres and do not reflect the overall pattern of practice in a defined population.

Referral patterns should therefore change. Early endoscopic assessment should be encouraged, such that patients with any symptoms referable to the upper gastrointestinal tract are investigated, as opposed to only those with the established symptoms of gastric cancer who commonly have advanced disease and currently comprise the group referred for endoscopy. It is not possible, however, to be more specific about the important symptoms, as studies from our programme for the early detection of disease[14] have failed to correlate any symptom with the extent of disease[15].

The high proportion of patients with advanced disease is reflected in the poor overall survival, which differs little from the previous report from this registry[1]. However, the improvement in survival for curative resection does offer some encouragement. As the operative mortality has shown little change throughout the study period, the explanation for this improving trend is conjectural. Preoperative assessment and postoperative support may be important, although these would be expected to influence operative mortality. It is possible that anaesthetic advances have allowed more radical procedures to be undertaken and thus, for those surviving the operation, greater tumour clearance has increased the chances of disease-free survival.

The numbers of patients dying in the postoperative period is of particular concern, especially in the context of the current Medical Research Council trial of extended gastrectomy and lymphadenectomy[9]. The results of the analysis of the frequency of gastric resection by individual surgeons highlight the importance of experience, particularly in total gastrectomy. Whether this is a reflection of technical expertise, better patient selection or improved pre- and postoperative management is difficult to determine from a retrospective study such as this Nevertheless, the operative mortality rates achieved by those surgeons in the West Midlands most frequently performing total gastrectomy compares poorly with that reported by specialist centres in Europe and Japan. Pichlmayr and Meyer[16] in the FRG report an operative mortality rate for total gastrectomy of 8 per cent and the overall Japanese figure is 3 per cent[17]. Furthermore, recent series from individual surgeons with an interest in gastric surgery clearly demonstrate acceptably low operative mortality rates following radical resection. In personal series of radical resections from UK surgeons, operative mortality rates of 5 per cent[18] and zero[19] have been reported. In addition, a 30-year study from one institution in the USA describes an operative mortality rate of 11 per cent for curative gastrectomy associated with a curative resection rate of 1·6 procedures per year[20]. Thus, although operator frequency may in part improve operative mortality rates, a strong case can be made for the development of specialist referral centres in which interested, experienced surgeons with appropriate supporting staff are regularly undertaking radical resections. This would enable standardization of management, surgical procedure and pathological documentation not only to produce the optimal outcome for our patients but also to improve understanding of the natural history of gastric cancer

Gastric cancer remains a major management problem. This study has described treatment and results which are probably typical for the whole country. Improvements are only likely with earlier detection and, with the current incidence of disease, this can only be applied to symptomatic patients. Nevertheless, early assessment of any upper gastrointestinal symptom needs to be emphasized to all involved in the management of such patients. In addition, for such an approach to succeed the early results of curative surgery need to be free from major morbidity and mortality and should only be performed in specialized centres.

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Technique for abdominal radical total gastrectomy

J. F. Chester and J.-C. Gazet

St. George's Hospital, Blackshaw Road, London SW17 0QT, UK

Correspondence to: Mr J.-C. Gazet

Abdominal radical total gastrectomy for cancer involves mobilization of the stomach, spleen, greater omentum and contiguous lymph-drainage areas. Conventional dissection commences lateral to the spleen, which is mobilized medially, with subsequent stripping of peritoneum over the pancreas, and identification of the coeliac trunk and left gastric artery. The dissection proceeds along the greater and lesser curves of the stomach after division of the omental attachments to the colon, and the duodenum is divided distal to the pylorus. Division of the oesophagus is usually undertaken immediately before delivery of the specimen.

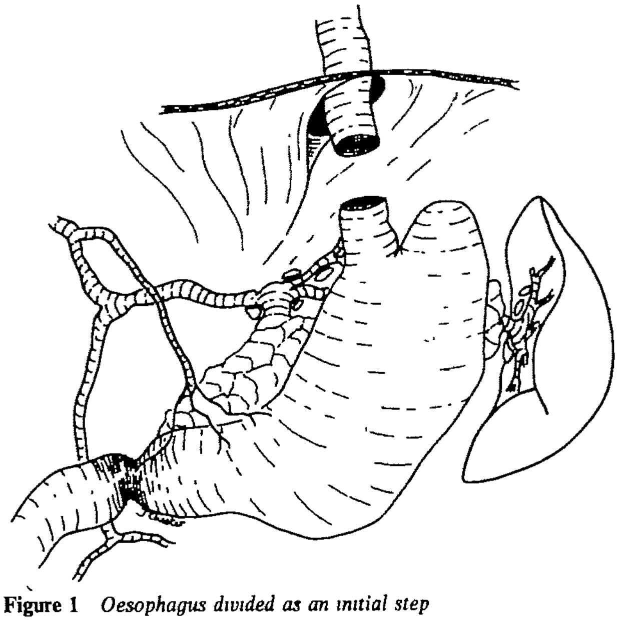

Figure 1 *Oesophagus divided as an initial step*

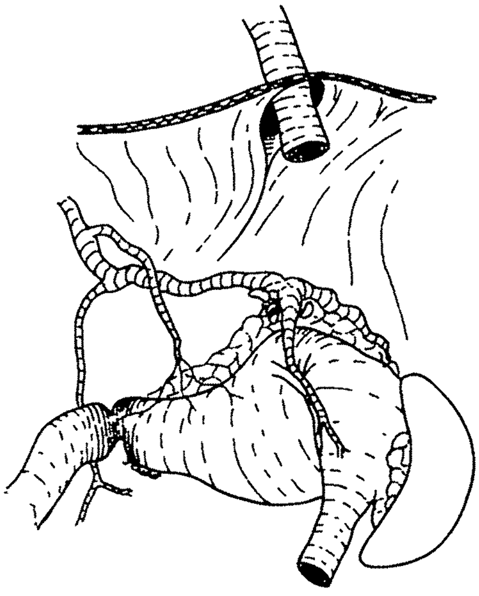

Figure 2 *Specimen displaced to display coeliac trunk and left gastric artery*

Technique

Our modification of abdominal radical total gastrectomy, which has now been used in over 100 patients, involves an initial assessment and confirmation of operability, with subsequent immediate mobilization and division of the oesophagus at the diaphragmatic hiatus (*Figure 1*). Inferomedial displacement of the specimen after division of the lienorenal ligament and mobilization of the spleen is then undertaken Using this technique, the left gastric artery and coeliac trunk are easily identified (*Figure 2*), and delivery of the stomach and surrounding lymphatic drainage areas is safer, quicker and easier.

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Controlled trial of heater probe treatment in bleeding peptic ulcers

A prospective randomized controlled trial of endoscopic heater probe therapy in bleeding peptic ulcers was performed to determine whether probe therapy can reduce rebleeding rates. Of 630 patients endoscoped for suspected upper gastrointestinal haemorrhage over a 16-month period, 166 (26 per cent) were found to have a peptic ulcer. Either minor or no stigmata of recent haemorrhage were found in 115 patients at the time of endoscopy. A single peptic ulcer with either active haemorrhage or a visible vessel was found in 51 patients, 43 of whom were entered into the trial. There were eight exclusions: four were inaccessible, one was a torrential haemorrhage and three were excluded for non-technical reasons. Patients were randomized to receive either heater probe ($n = 20$) *or sham* ($n = 23$) *therapy. In actively bleeding ulcers, immediate haemostasis was achieved following probe therapy in 14 of 18 patients (78 per cent) compared with none of 21 having sham treatment* ($P < 0{\cdot}002$). *No rebleeding occurred in the probe therapy group* ($n = 20$) *compared with rebleeding in five of 23 sham treated patients* ($P = 0{\cdot}05$). *Urgent surgery for haemostasis was required in three of the five sham treated patients who rebled. It is concluded that heater probe therapy may be effective in reducing rebleeding rates in peptic ulcers accessible to the endoscope.*

G. M. Fullarton,
G. G. Birnie*,
A. Macdonald and
W. R. Murray

University Department of Surgery,
Western Infirmary, Glasgow and
**King's Mill Hospital, Sutton-in-Ashfield, Nottinghamshire, UK*
Correspondence to:
Mr G. M. Fullarton, University
Department of Surgery, Western
Infirmary, Glasgow G11 6NT, UK

Keywords: Peptic ulcer haemorrhage, endoscopic therapy, heater probe

The mortality rate of upper gastrointestinal haemorrhage remains around 10 per cent despite advances in diagnostic and resuscitation techniques[1,2]. Much of this mortality relates to rebleeding in an increasingly elderly population[2]. If advances are to be made in the treatment of these high-risk patients, satisfactory non-operative methods of preventing rebleeding must be developed. Of the currently available endoscopic thermal methods only the laser has shown clear benefit[3–6]. Lasers, however, are expensive, non-portable and are unlikely to be widely available. The heater probe is a transendoscopic thermal device which is relatively inexpensive, portable and, in experimental tests, produces vessel coagulation with less tissue erosion than seen with other currently available thermal devices[7–9].

A prospective, randomized controlled study assessing the efficacy of the heater probe in the management of patients with bleeding peptic ulcers is reported.

Patients and methods

All patients admitted to the Western Infirmary, Glasgow with acute upper gastrointestinal haemorrhage over the 16-month period of the trial (from August 1986 to November 1987) were considered for inclusion. Patients presenting with haematemesis and/or melaena routinely had endoscopy within 24 h of admission by an experienced member of the Haematemesis Management Team. Potentially eligible patients were diagnosed endoscopically to have a single peptic ulcer in the stomach, pyloric canal or duodenal cap, and no other significant upper gastrointestinal source of blood loss such as oesophageal varices, carcinoma or multiple bleeding erosions. When a patient was recognized to be potentially eligible for study entry, the ulcer was assessed by the heater probe endoscopist (G.M.F.). The patient was only deemed eligible for entry into the study if the following criteria were also met: (1) actively bleeding sites on the ulcer before or after washing, and/or (2) a visible vessel in the ulcer base before or after washing, and (3) confirmed accessibility of the heater probe to the source of blood loss. Active bleeding was defined as a continuous flow of blood from the ulcer base continuing for the duration of the endoscopy. A visible vessel was defined as an elevated red or blue spot, a pulsatile pseudoaneurysm or active arterial spurting. These endoscopic criteria are known to be associated with the highest risk of rebleeding[10–13].

Patients who fulfilled these criteria were then stratified for age (<60 and ⩾60 years), shock (systolic blood pressure <100 mmHg, pulse >100/min: present/absent on admission) and ulcer site (gastric/duodenal). Randomization was carried out within each group, a sealed envelope being opened to indicate either heater probe or sham therapy.

Heater probe therapy was performed by a single operator (G.M.F.) using an Olympus GIT-IT10® (Olympus Corporation, Tokyo, Japan) endoscope and Olympus Heatprobe Unit with CD 10Z heater probe (3·2 mm outer tip diameter; *Figure 1*). The heater probe is an endoscopic contact thermal device which has an internal silicon chip controlled heating element linked to a computerized power source. Thermal energy is transferred by conduction through the probe tip at variable energy settings (5–30 J) each delivered as a 7-s pulse. The probe tip is Teflon® (E. I. du Pont de Nemours and Company, UK) coated which reduces tissue adherence.

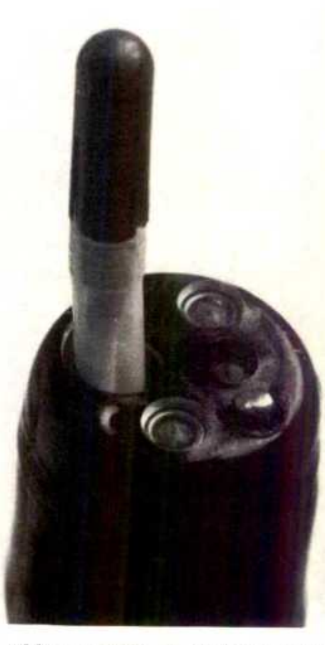

Figure 1 *View of heater probe tip (3·2 mm outer diameter) with an Olympus GIF-IT10 endoscope*

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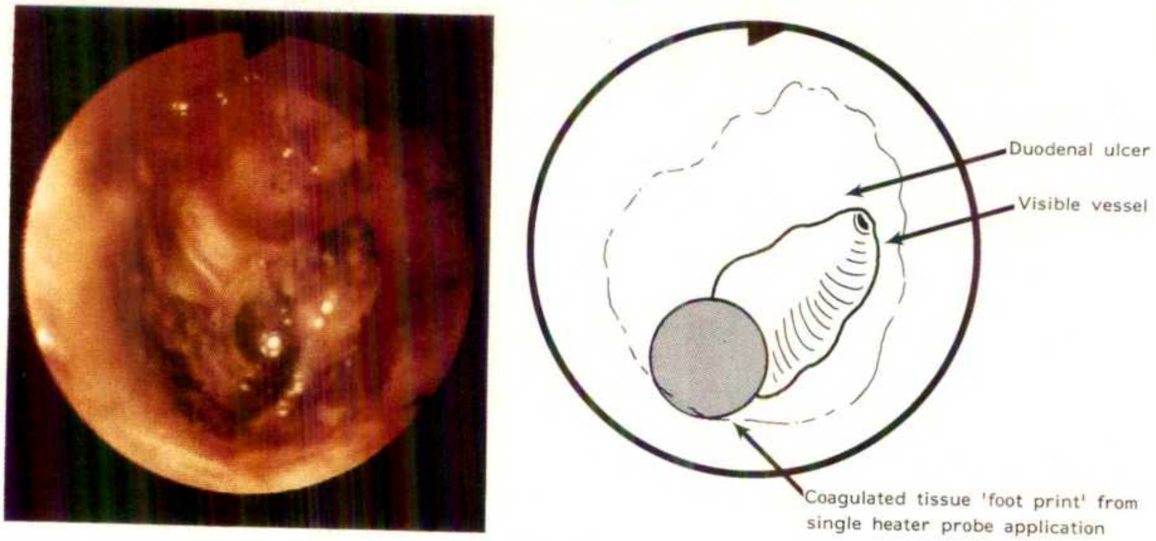
Duodenal ulcer
Visible vessel
Coagulated tissue 'foot print' from single heater probe application

Figure 2 *Endoscopic appearance of a visible vessel in a duodenal ulcer base after a single heater probe application*

The heater probe technique used was that recommended by Johnston *et al.*[14]. With active haemorrhage, the probe was used to tamponade the bleeding point until haemostasis was achieved. The probe, through its proximal water ports, allowed continuous washing during tamponade which helped to indicate when haemostasis had been successful. The heater probe was then activated at the 25 J setting and further therapy applied until complete haemostasis was secured. In the absence of active bleeding, a clot overlying an ulcer was washed until the underlying bleeding point or visible vessel was seen. After this, cautery was applied as described above (*Figure 2*). On average seven applications per patient, delivered at a 25–30 J setting, were required to achieve complete haemostasis. The maximum number of applications in any patient was ten at the 25 J setting. Sham therapy consisted of the heater probe being held inactivated in the gut lumen. Only the endoscopist was aware of which treatment each patient had received and he took no further part in their management.

Following endoscopy, patients were managed by members of the team unaware of the initial randomization, and their progress was documented until discharge or death. All patients received H_2-receptor antagonist therapy (ranitidine 50 mg IV 6-hourly) and blood transfusion where deemed appropriate by the attending clinician. Rebleeding was diagnosed by team members if one of the following features was present:

1. Fresh blood in the upper gastrointestinal tract at re-endoscopy or surgery
2. Vomiting fresh blood at any time other than immediately after endoscopy where fresh blood had been noted
3. Fresh melaena plus one of the following:
   (a) Haemodynamic and clinical evidence of hypovolaemic shock (systolic blood pressure < 100 mmHg, pulse rate > 100/min)
   (b) A falling haemoglobin despite blood transfusion (failure to raise haemoglobin by more than 0·5 g/dl per unit of blood transfused).

Surgical intervention for haemostasis was undertaken when deemed appropriate by the attending surgeon.

Quantitative data (expressed as mean ± s.e.m.) were analysed by the unpaired, two-sided Wilcoxon rank sum test. Integral data were compared by the Fisher's exact test. Significance was taken at the 5 per cent level ($P \leqslant 0{\cdot}05$).

All patients gave written, informed consent and the study was approved by the local hospital ethical committee.

Results

During the 16-month trial period (from August 1986 to November 1987), 630 patients presenting with suspected acute upper gastrointestinal haemorrhage had endoscopy within 24 h of presentation to the Western Infirmary, Glasgow. One hundred and sixty-six (26 per cent) were found to have a peptic ulcer. Of these, 115 (69 per cent) had either no stigmata of recent haemorrhage or minor stigmata (flat black/red spots) at the time of endoscopy. This group was deemed a low-risk group in terms of rebleeding but their progress was also documented until discharge. None of these patients rebled. A single peptic ulcer with either active haemorrhage or a visible vessel was found in 51 patients, 43 of whom were entered into the trial. There were eight exclusions: four high, lesser curve gastric ulcers were inaccessible to endoscopic treatment and were therefore not randomized; the endoscopist was not available for two patients; in one patient there was torrential arterial haemorrhage from a posterior wall duodenal ulcer necessitating immediate surgery; and in one patient the attending surgeon had decided on immediate surgery after endoscopy and therefore this patient was not randomized. Of the four patients excluded because of inaccessibility, four rebled, three required emergency surgery for haemostasis and two died.

Of the 43 patients entered into the trial 20 were randomized to receive heater probe therapy and 23 sham therapy. Both groups were well matched with regard to clinical and endoscopic criteria known to influence prognosis (*Table 1*). Nine patients in the heater probe group and nine patients in the sham group had serious coincidental disease.

In patients actively bleeding at the time of endoscopy, immediate haemostasis was achieved in 14 of 18 heater probe patients compared with none of 21 patients having sham treatment ($P < 0{\cdot}002$). The post-treatment blood transfusion requirements (units packed cells) were 1·7 ± 0·4 (mean ± s.e.m.) in the probe group and 2·8 ± 0·6 in the sham group. Mean non-operative hospital stay (mean ± s.e.m.) was 4·1 ± 0·2 days in the probe group and 4·4 ± 0·4 days in the sham group. No rebleeding occurred in the probe treated group ($n = 20$) while five of the 23 sham treated patients rebled ($P = 0{\cdot}05$). Surgery for haemostasis was required in three of these five sham treated patients who rebled. No patient died.

When endoscopic characteristics were assessed, none of the seven ulcers with visible vessels rebled in the heater probe group while three of four rebled in the sham treated group. Considering all untreated ulcers with a visible vessel in the study, seven of eight (88 per cent) rebled, compared with none of the seven having probe therapy ($P < 0{\cdot}04$). In ulcers with active oozing, none of the 13 in the probe group rebled while two of 19 rebled in the sham group.

One perforation occurred 3 h after heater probe treatment in a 76-year-old man who had an actively bleeding anterior wall duodenal ulcer. He had prolonged endoscopy and had a total probe application of 250 J. At laparotomy, a clean acute anterior duodenal perforation was noted with no macroscopic evidence of thermal-induced perforation. A truncal vagotomy and pyloroplasty were performed and he made an uncomplicated recovery.

Table 1 *Clinical and endoscopic characteristics of the study groups*

	Sham ($n = 23$)	Heater probe ($n = 20$)
Mean age (years)	52·8 (4·3)	57·2 (4·1)
Range	18–89	24–76
Mean admission haemoglobin (g/dl)	11·0 (0·5)	10·0 (0·6)
Range	4·5–14·5	5·5–14·6
Mean pretreatment blood transfusion (units PC)	1·2 (0·3)	1·3 (0·3)
Range	0–4	0–3
Ulcer site		
Gastric	7	8
Duodenal	16	12
Endoscopic features		
Active oozing	19	13
Bleeding vessel	2	5
Non-bleeding vessel	2	2

Values in parentheses are s.e.m. PC, packet cells

Discussion

This study has demonstrated that heater probe therapy reduces rebleeding rates in patients presenting with acute upper gastrointestinal haemorrhage from peptic ulcers with endoscopic criteria suggesting a high risk of rebleeding.

As the population presenting with acute upper gastrointestinal haemorrhage ages, there is a need for a simple, inexpensive and effective endoscopic therapy for peptic ulcer haemorrhage. Endoscopic injection therapy with adrenaline and polidocanol[15] or adrenaline alone[16] has recently been used to treat peptic ulcer haemorrhage and has shown convincing benefit in producing immediate haemostasis and reducing the requirement for emergency surgery. Further controlled studies assessing these treatment regimes are required to confirm these findings. The heater probe is small, portable and relatively inexpensive (6200 pounds sterling). In addition, it has specific technical advantages over other currently available endoscopic thermal devices. Firstly, it has a powerful washing facility which, by improving visibility, allows accurate targeted therapy, directly on to the bleeding site. Secondly, the heater probe produces coagulation by combining heat and pressure simultaneously (coaptive coagulation) resulting in more effective haemostasis with less tissue erosion[9]. This compares favourably with laser photocoagulation which requires tissue heating alone to induce vessel shrinkage (zonal heating)[9]. Thirdly, the probe, unlike other thermal devices, can be applied and activated tangentially, allowing better access to difficult ulcers. Disadvantages encountered with the heater probe are few, although with any device requiring physical pressure to produce vessel tamponade there is always the risk, albeit small, of visceral perforation. Several experimental studies have confirmed the heater probe to be the safest and most effective thermal device currently available[7–9]. In our study the maximum energy application to any patient was 250 J (10 × 25 J), although increased energy loads have been reported in the treatment of peptic ulcer bleeding without complications[14,17].

The results of our study differ from a preliminary report by Matthewson and his colleagues where a laser, but not a heater probe, showed a benefit over controls[18]. The studies are not entirely comparable in that their randomization was biased towards probe therapy and, in addition, data from previous laser work were recruited to improve the significance of laser over probe treatment. A previous uncontrolled study by Johnston *et al.* showed the probe to be more effective than the Nd-YAG laser in producing haemostasis[14].

In evaluating new endoscopic therapeutic methods in upper gastrointestinal haemorrhage it is important to identify and study only patients at high risk of rebleeding, where benefit from an interventional treatment regime may be seen early. Our study evaluated only patients who were either actively bleeding or who had visible vessels, both high-risk factors in predicting rebleeding[11–13]. In our study the rebleeding rate of untreated visible vessels was 88 per cent, confirming the significance of this endoscopic feature. In contrast, no rebleeding was noted in the seven visible vessels treated with the heater probe, emphasizing the efficacy of the probe in treating these lesions.

The single operator aspect of our study is another feature which deserves emphasis, particularly in discussing the assessment of new endoscopic techniques. A single operator study will contain less 'learning period' bias than an equivalent multioperator trial and should therefore provide a more accurate evaluation of the technique. This view is supported by previous single operator studies[5,19] where the overall results using identical equipment tend to be better than in similarly designed multioperator trials[20–22]. Any new endoscopic thermal device should be sufficiently simple and effective to be used in the clinical situation by several operators. The heater probe fulfils these criteria and, since the end of the current study, has been used effectively by other endoscopists.

Although our study showed a reduction in rebleeding rates following heater probe therapy, we also noted a small group of patients with endoscopically inaccessible ulcers who fared particularly badly, with a high rebleeding and operation rate. Ulcer inaccessibility has also been a consistent problem in other studies assessing varying endoscopic methods[3,5,19–21] and is clearly the limiting factor with most of the currently available endoscopic techniques. Accessibility may be improved by developments in therapeutic endoscopes or modifications of the thermal devices themselves.

We feel that heater probe therapy is of significant benefit in the treatment of patients with major peptic ulcer haemorrhage, although this will require confirmation in further controlled trials. The heater probe size and cost make this device a practical proposition for all units involved in the management of peptic ulcer related upper gastrointestinal haemorrhage.

Acknowledgements

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545–548

Vascularization of small liver metastases

The portal vein contributes little to the blood supply of established liver metastases in the presence of a patent hepatic artery. However, its role in the perfusion of early metastatic liver disease remains controversial. We have quantified the relative contribution of the portal vein and hepatic artery to the internal circulation of small liver tumours. These studies were conducted in a new rat model of liver metastases generated by the intraportal injection of cultured tumour spheroids. A total of 633 lesions were studied in 18 animals using radioisotope tracer microspheres. Nodules ranged from 0·5 to 6·0 mm in diameter, 92 per cent being 3·0 mm or less. The ratio of radioactivity in tumour compared with normal tissue (T:N ratio) was determined after simultaneously injecting microspheres into the portal and arterial circulation of each animal. The mean hepatic artery T:N ratio was significantly greater than that of the portal vein for all tumour sizes studied (P < *0·01). Nodules 0·5 mm in diameter had a mean (s.e.m.) hepatic artery T:N ratio of 1·50 (0·12) in comparison with a mean portal vein ratio of 0·13 (0·04). Tumour nodules 2·0 mm in diameter had a mean (s.e.m.) hepatic artery T:N ratio of 1·26 (0·11) in comparison with a mean portal vein ratio of 0·06 (0·01). The overall T:N ratio for both routes decreased with increasing tumour size. These results indicate that hepatic tumours as small as 0·5 mm already have an established internal vasculature perfused predominantly by the hepatic artery. In contrast, the portal vein contributes insignificantly to the internal perfusion of these lesions. These results have significant implications for adjuvant locoregional therapy in gastrointestinal cancer.*

Keywords: Liver, metastases, vascularity

S. G. Archer and
B. N. Gray

University Department of Surgery,
Royal Perth Hospital, Perth,
Western Australia 6000, Australia
Correspondence to:
Dr S. G. Archer

The role of the portal vein in the perfusion of liver metastases is controversial. It has been shown both experimentally and clinically that it has little function in the nutrition of large tumours in the presence of a patent hepatic artery[1–3]. In contrast, the contribution of the portal venous circulation to the nutrition of early metastatic liver disease is poorly understood. Whilst there is agreement that it nourishes micrometastases by diffusion, the evidence for direct portal vascularization of small clinically undetectable liver metastases is conflicting[4–9]. This must be quantified in order to understand the full potential of adjuvant therapy in gastrointestinal cancer.

The study of blood flow in small liver metastases in patients is not possible with the limited resolution of present imaging techniques. Accordingly, clinical data relate to relatively large lesions, in which the hepatic artery has been shown to be the major blood supply[4]. Metastatic liver disease has been studied in patients at post-mortem examination, but these results may not reflect perfusion under physiological conditions. Nevertheless, injection studies in cadaver specimens demonstrate a mixed circulation in metastases less than 1·0 cm in size in which the arterial component predominates[5,6].

Perfusion of small liver tumours has been assessed in a number of experimental animal models. Tumours generated in rats by direct intrahepatic implantation have been shown to derive part of their blood supply from portally filled vessels either within or encircling the lesion[7,8]. Hepatic arterial ingrowth is well established by the time these lesions reach 2·0 mm in diameter[7,8]. Similarly, chemically-induced primary hepatocellular carcinomas in rats seem to derive nutritive flow from the portal vein up to a size of 2·0 mm[9].

Although the above studies suggest at least some portal vein perfusion of liver metastases up to a few millimetres in size, they do not quantify this in relation to the hepatic artery. As the perfusion characteristics of tumours can vary widely, a large number of lesions of comparable size need to be assessed. We have achieved these aims in a rat model of liver metastases generated by the intraportal injection of cultured tumour spheroids.

Materials and methods

Animals

Inbred male Wistar WAG rats weighing between 250 and 280 g were obtained from the Animal Resources Centre at Murdoch University, Western Australia. The animals were fed standard rat pellets and water *ab libitum* and allowed a period of 7 days acclimatization. All experiments on animals were conducted in accordance with the guide-lines of the National Health and Medical Research Council of Australia.

Cell culture on microspheres

The cell line 192 NRc was derived from a 1,2-dimethylhydrazine (DMH)-induced colonic carcinoma in Wistar WAG rats. The supply of tumour for culture was established by intramuscular hindlimb implantation and freezing down a large quantity of solid material at −70°C from the second passage generation.

Microspheres used for culture were positively charged polystyrene ion exchange resins (Dowex 2, The Dow Chemical Company, USA), sized to 45–75 μm in diameter Equal aliquots of microspheres were washed in Hank's solution (without Ca^{2+}, Mg^{2+}) and then autoclaved When cultured with RPMI 1640 media (Flow Laboratories, North Ryde, New South Wales, Australia), penicillin 100 units/ml, streptomycin 100 μg/ml and 5 per cent fetal bovine serum, the cells covered each microsphere in a firmly attached monolayer. The tumour spheroids were washed in RPMI 1640 to remove free cells from suspension and diluted to an appropriate concentration for injection.

Induction of liver metastases

The detailed description of this model has been previously reported[10]. The portal vein of 18 rats was injected with either 5×10^4 or 1×10^5

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Table 1 *Hepatic tumour perfusion*

Rat No	Days*	Number of tumours	Mean diameter (mm)	Mean hepatic artery T:N ratio	Mean portal vein T.N ratio	*P* value†
1	12	15	0·80 (0·08)	0·90 (0·15)	0·14 (0·07)	<0·01
2	11	41	0·94 (0·06)	1·67 (0·16)	0·08 (0·01)	<0·01
3	12	103	1·02 (0·05)	1·26 (0·12)	0·04 (0·01)	<0·01
4	12	54	1·04 (0·06)	1·06 (0·08)	0·02 (0·01)	<0·01
5	12	40	1·12 (0·06)	1·08 (0·06)	0·17 (0·08)	<0·01
6	13	23	1·13 (0·08)	0·99 (0·15)	0·06 (0·03)	<0·01
7	12	12	1·17 (0·16)	1·58 (0·27)	0·04 (0·01)	<0·01
8	12	38	1·41 (0·10)	0·82 (0·13)	0·10 (0·02)	<0·01
9	12	120	1·85 (0·08)	1·38 (0·14)	0·14 (0·04)	<0·01
10	17	25	2·00 (0·16)	1·22 (0·18)	0·03 (0·01)	<0·01
11	17	4	2·00 (0·00)	0·73 (0·17)	0·06 (0·02)	0·07
12	14	85	2·42 (0·14)	0·94 (0·12)	0·02 (0·01)	<0·01
13	16	9	2·67 (0·61)	1·69 (0·34)	0·06 (0·01)	<0·01
14	15	21	2·71 (0·29)	0·60 (0·09)	0·05 (0·02)	<0·01
15	16	6	2·83 (0·40)	2·78 (0·42)	0·27 (0·08)	0·03
16	17	18	2·94 (0·38)	1·05 (0·18)	0·04 (0·01)	<0·01
17	19	11	3·64 (0·56)	0·91 (0·18)	0·04 (0·02)	<0·01
18	19	8	4·75 (0·37)	0·77 (0·10)	0·02 (0·01)	0·02

*Days from tumour inoculation; †T:N ratios for hepatic artery and portal vein compared, values in parentheses are s.e.m.

tumour spheroids to produce discrete hepatic tumours in varying numbers. Perfusion of tumour nodules was assessed over a time period ranging from 11 to 19 days after inoculation of the cancer spheroids. The growth characteristics of this model indicate that lesions sampled during this time interval would range from 0·5 to 7·0 mm in diameter[10].

Blood flow measurements

A standard tracer microsphere technique was used to quantify the perfusion of individual tumours. The carotid artery and portal vein of each animal was cannulated with a polyethylene catheter (SP8, Dural Plastics and Engineering, Auburn, Australia). A homogeneous suspension of radioisotope-labelled microspheres was obtained by mixing between two syringes through a three way tap. Simultaneous injections over 30 s of 2×10^6 ^{57}Co and 6×10^5 ^{113}Sn or ^{125}I microspheres were administered into the left ventricle and portal vein respectively.

Preliminary experiments in normal animals confirmed that there was maximal trapping of tracer microspheres in tissue. After left ventricular injection of microspheres, 0·2 per cent of the total counts in the gastrointestinal tract were detected in portal blood. Similarly, only 0·01 per cent of the total liver counts were detected in systemic arterial blood after portal vein administration.

Tracer sphere injections into the portal venous and hepatic arterial circulation of tumour-bearing animals were carried out as described above. Five minutes later, 1·0 ml 50 per cent Indian ink (Reeves Educational Colours, Pty Ltd., Victoria, Australia) was infused into the inferior vena cava to demarcate hepatic tumour nodules. The carbon particles in the ink are phagocytosed by the Kupffer cells of the reticuloendothelial system of normal liver parenchyma. The livers were removed and fixed in Fekete's solution (formalin, acetic acid and ethyl alcohol). Individual lobes were separated and sectioned at 1·0-mm intervals, tumour appearing as discrete white nodules against a dark parenchymal background.

Nodules were dissected out under magnification, care being taken to remove all adherent liver tissue. The maximum diameter of each tumour was recorded to the nearest 0·5 mm and its mass determined to within ±0·05 mg (Sartorius balance, Sartorius-Instruments Ltd., UK). The activity for each isotope was measured in a three channel γ counter (Packard Instrument International S.A., Zurich, Switzerland). Individual tumour nodules and the normal liver tissue from each lobe were counted separately.

Relative perfusion of tumour nodules was expressed as the ratio of the weight specific counts for the lesion and the normal liver tissue from the lobe of origin (T.N ratio).

Statistics

The statistical significance of observed differences between the portal vein and hepatic artery T.N ratios were analysed using a two-tailed Wilcoxon signed rank test.

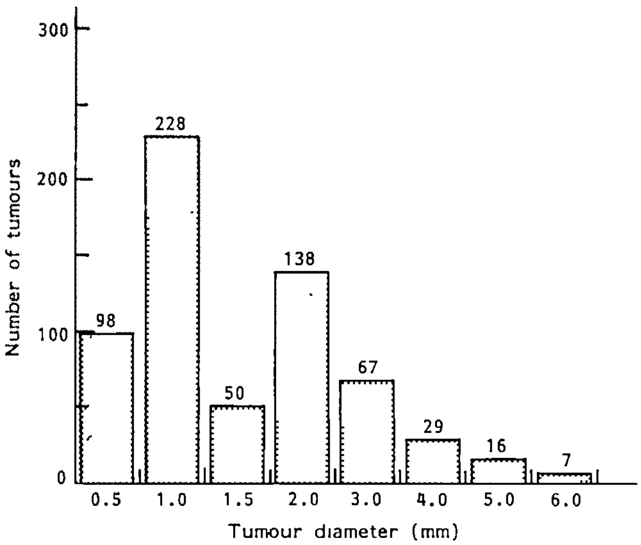

Figure 1 *Frequency distribution of 633 liver tumours examined in 18 rats according to tumour size*

Results

Tumour growth

All animals injected with tumour spheroids developed multiple hepatic nodules. The total number of liver tumours in each of the 18 animals studied varied from a minimum of four to a maximum of 120 (*Table 1*). Rats killed at 12 days from inoculation had a mean (s.e.m.) tumour diameter of 1·33 mm (0·04). Nodules studied at 19 days had a mean diameter of 4·1 mm (0·37). Relative perfusion was assessed in a total of 633 tumours ranging from 0·5 to 6·0 mm in diameter. Their distribution according to diameter is illustrated in the frequency histogram in *Figure 1*. Of the tumours, 92 per cent were 3·0 mm or less in diameter.

Blood flow studies

Injections of tracer microspheres via either vascular route resulted in excess of 10^4 spheres per gram of normal liver tissue. *Table 1* lists the mean hepatic artery and portal vein T·N ratios for each animal. The mean T·N ratios following portal vein administration were all $\leqslant 0·27$. In contrast, the mean hepatic

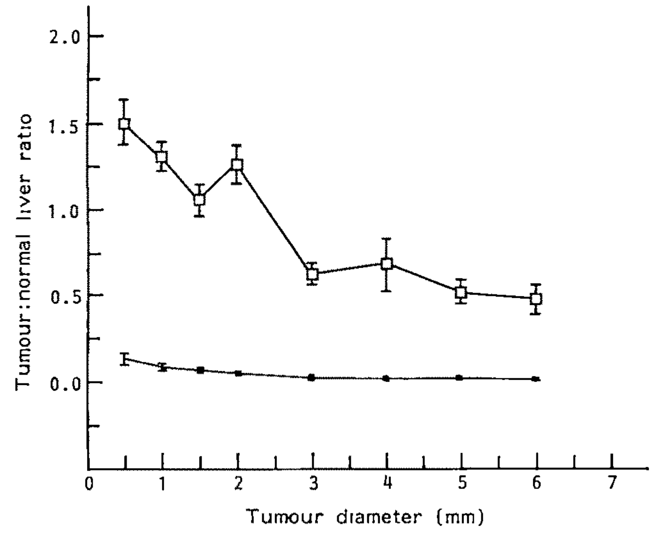

Figure 2 *Tumour normal liver ratios after injection of radioactive tracer microspheres into the arterial (□) and portal venous (—) circulation of each animal; each point is the mean and standard error of all tumours studied at that diameter*

artery T·N ratio was significantly greater than that for the portal vein in all animals, the lowest mean value being 0 6 (rat 14).

The relationship between perfusion and tumour size is illustrated in *Figure 2* where the data for all animals have been combined. There is about a 20-fold difference between the mean portal and hepatic T·N ratios at all tumour diameters ($P < 0{\cdot}01$). These results indicate that small 'secondary' liver tumours were not significantly vascularized by the portal vein. In contrast, the smallest lesions studied (0·5 mm) had an established internal circulation perfused predominantly by the hepatic artery (mean T:N ratio of 1·50). As diameter increased, overall tumour vascularity diminished. Nodules greater than 2 0 mm in diameter were hypovascular in comparison to the normal liver parenchyma. There was no histological evidence of tumour necrosis in the larger tumours.

Discussion

A study of the perfusion of small experimental liver metastases has been carried out in Wistar WAG rats. Multiple discrete liver tumours were produced in these animals by the injection of tumour spheroids into the portal vein. Spheroids were obtained by the culture of a DMH-induced colonic carcinoma cell line on to the surface of polystyrene microspheres. Using a standard radioisotopic microsphere technique, we have been able to quantify the relative perfusion of 633 tumour nodules ranging from 0·5 to 6·0 mm in diameter.

The most important finding has been that there was negligible trapping of microspheres in small liver tumours following portal vein injection (mean T.N ratios $\leqslant 0{\cdot}13$). In contrast, the smallest lesions studied (0·5 mm) had already developed a rich internal circulation perfused almost exclusively by the hepatic artery (mean T:N ratio 1·50).

Other experimental studies investigating the role of the portal vein in the perfusion of small liver tumours differ in their findings. Conway *et al.* demonstrated diffusion of portal nutrients into chemically-induced hepatocellular carcinomas up to 2·0 mm in diameter in rats using optical and polarographic techniques[9]. Furthermore, Nilsson and Zettergren demonstrated filling of these primary lesions in the same model using barium sulphate portography[11]. Although this model allows the study of small tumours in the liver, the lesions have not arisen by dissemination. Therefore, it would be inappropriate to draw the same conclusions about portal vascularization in small liver metastases.

Experimental models in which liver metastases are generated by the intravascular injection of single cancer cells have been used for studying metastatic liver disease. Using this transplantation technique in rabbits and mice, Breedis and Young noted minimal filling of liver tumours following portal injection of Indian ink[5]. Similarly, Blanchard *et al.* drew the same conclusion using a radioactive microsphere technique[12] Although the diameter of the experimental lesions in both these studies was not specified, the methodology suggests that they were relatively large

The studies of Ackerman using rat sarcomas implanted directly into liver parenchyma show tumours < 1·0 mm as blank spaces in the liver[7,8]. In some of the 1 0–2·0 mm tumours, predominant filling of vessels with dyes following portal vein injection could be demonstrated. Only when lesions reached 2·0 mm did an arterial circulation seem to be well established. This apparent delay in hepatic artery vascularization (in comparison with our findings) may be artefactual owing to the size of the original tumour implants. Furthermore, the liver trauma associated with direct tumour implantation will result in an inflammatory and healing response which may influence the process of new vessel formation. Our technique of generation of small liver metastases is a better physiological correlate. It is probable that our findings more closely reflect the development of tumour circulation in early disease.

We have shown that metastatic lesions less than 2·0 mm in diameter are more vascular than the surrounding liver parenchyma. Lesions larger than this were on the whole hypovascular by comparison, despite the absence of histological evidence of tumour necrosis. The phenomenon of diminishing tumour vascularity with tumour growth has been well described. This observation has been attributed to progressive hypovascularity of the tumour centre with the maintenance of a hypervascular rim[13]

The clinical relevance of our experimental study is supported by the human post-mortem findings of other investigators. Breedis and Young observed a predominant arterial supply to liver metastases as small as 0·5–1·0 mm in patients who died from disseminated colonic carcinoma[5]. Lin *et al.* noted that portal vein branches often ended abruptly at the tumour periphery, suggesting that these thin-walled vessels had become compressed and obliterated[6].

Our findings have significant implications for the design of clinical trials in adjuvant chemotherapy in gastrointestinal cancer. Regional therapy administered into the portal vein is now being investigated as an adjuvant treatment for colorectal cancer[14,15]. Its aim is to treat metastatic liver disease which is clinically undetectable at the time of surgery. As our study shows minimal internal tumour perfusion by the portal vein, it is likely that this form of treatment will rely on penetration of anticancer agents into tumour tissue from the external vasculature. The size of occult liver metastases may therefore be an important limiting factor in therapy via this route. Patients who appear to be free of liver metastases at the time of surgery may in fact harbour lesions ranging in size from single cells to small metastases a few millimetres in diameter. Our studies indicate that many of these early metastases may already have a well developed arterial blood supply. It follows that chemotherapy via the portal vein will be incompletely effective in preventing the development of liver metastases. However, an improved response to regional chemotherapy might be expected if both the portal vein and hepatic artery were used for drug administration in the adjuvant setting.

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Case report

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Hepatic tumour resection with profound hypothermia and circulatory arrest

D. W. Goh, P. Gornall, K. D. Roberts*, R. Willetts* and M. C. G. Stevens†

*Departments of Paediatric Surgery, *Cardiothoracic Surgery and †Oncology, Birmingham Children's Hospital, Ladywood Middleway, Birmingham B16 8ET, UK*

Correspondence to: Mr D. W. Goh, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH, UK

Major hepatic tumour resection carries high mortality and morbidity rates primarily owing to massive haemorrhage. We have performed a right hepatic lobectomy for hepatocellular carcinoma using profound hypothermia and circulatory arrest. This technique was described by Ein *et al.* in 1981, and enables hepatic resection to be carried out in a bloodless field, thus offering the potential for resection of tumours which would otherwise be deemed unresectable[1]

Case report

An 8-year-old girl presented with abdominal pain, weight loss and gross hepatomegaly. Serum α-fetoprotein was markedly elevated (187 000 units/ml). An isotope liver scan showed irregular hepatomegaly with multiple defects. Abdominal ultrasonography showed large multinodular masses in the right lobe extending to the midline, with compression of the inferior vena cava. A needle biopsy showed a moderately differentiated hepatocellular carcinoma. Chemotherapy was commenced with Adriamycin® (Farmitalia Carlo Erba, St Albans, UK), vincristine, cisplatin and VP-16 (Vepesid®, Bristol–Myers, Slough, UK). The tumour responded to the chemotherapy with progressive falling of the serum α-fetoprotein and decrease in tumour size on ultrasonography. A computerized tomographic (CT) scan 4 months after commencing chemotherapy showed that the tumour in the inferomedial aspects of the right lobe was still large, and was compressing and surrounding the inferior vena cava. Chemotherapy was continued but 9 months after commencing treatment it became apparent that the tumour response had tapered off, and surgical resection was necessary.

A preliminary laparotomy was performed via a transverse upper abdominal incision to assess resectability. The tumour in the right hepatic lobe was large, partially surrounding and closely adherent to the inferior vena cava on its anterior and lateral aspects. The left lobe and porta hepatis were clear. The right hepatic artery, right branch of the portal vein and right hepatic duct were divided.

A median sternotomy was performed and the diaphragm was incised down to the inferior vena cava. After full heparinization, the right atrium was cannulated with a single cannula and the ascending aorta was cannulated. Cardiopulmonary bypass (*Figure 1*) was instituted at a flow rate of 2·4 litre $\text{m}^{-2}\,\text{min}^{-1}$ and a left ventricular vent was inserted. She was cooled down to a nasopharyngeal temperature of 17°C. Cold cardioplegia was used for myocardial protection. The systemic circulation was then stopped and the patient was exsanguinated into the extracorporeal circulation.

During circulatory arrest the tumour was dissected off the vena cava, the hepatic veins were divided and a right lobectomy was performed in a bloodless field. The margin of excision extended right up to the porta hepatis. Visible vessels and ducts were oversewn.

On completion of the resection she was rewarmed to a temperature of 34°C. Bypass was discontinued, decannulation and reversal of heparinization with protamine was carried out. The circulatory arrest time was 48 min.

The sternotomy and diaphragmatic incisions were closed and pericardial and anterior mediastinal drains were inserted. The abdominal incision was closed when satisfactory haemostasis was achieved.

Six hours postoperatively she had a further laparotomy because of abdominal bleeding. A bleeding point on the diaphragmatic suture line was found and controlled with diathermy. There was slight oozing from the raw edge of the liver and this was oversewn with an omental wrap. Subsequent recovery was uneventful.

The histology showed an hepatocellular carcinoma with tumour extending to the excision margin and neoplastic cells within large vascular channels.

Postoperatively she received two courses of VP-16 followed by a course of radiotherapy (2500 cGy) given to the whole volume of the regenerating liver, without complications.

Twenty months postoperatively she remains very well. CT scans and chest radiographs show no evidence of recurrence. Serum α-fetoprotein is undetectable.

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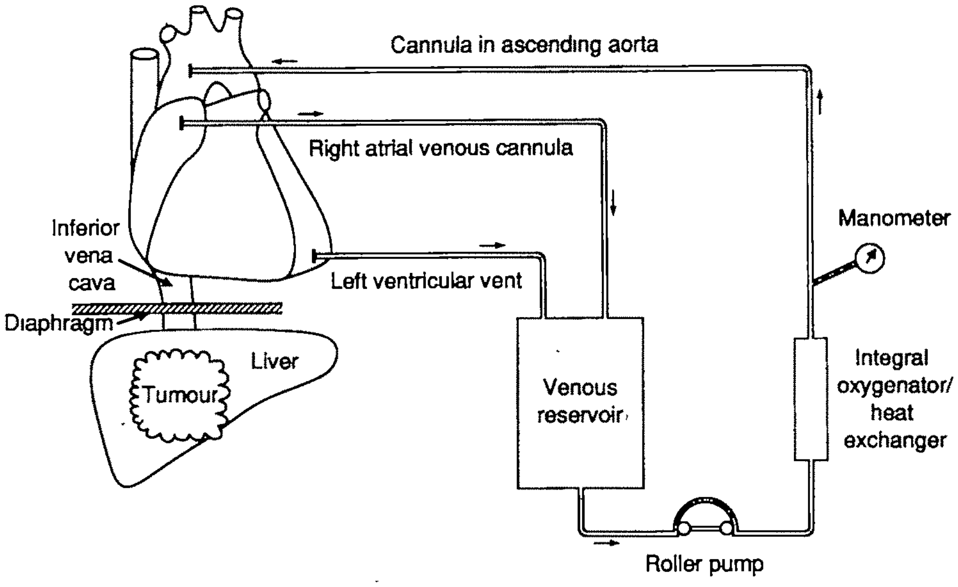

Figure 1 *Extracorporeal cardiopulmonary bypass circuit allowing induction of profound hypothermia and circulatory arrest*

Discussion

Major hepatic tumour resections in children are associated with a perioperative mortality rate of more than 11 per cent and a significant morbidity largely attributable to excessive blood loss[2]. Various techniques have been described in efforts to achieve adequate, safe hepatic resection with reduced blood loss. Hepatic resection utilizing normothermic hepatic vascular exclusion is based on the liver's ability to tolerate a warm ischaemia time of up to 1 hour[3]. This technique requires clamping of the abdominal aorta, suprahepatic and infrahepatic vena cava, portal triad, right adrenal vein and phrenic vein, which may prove difficult or impossible with large tumours involving the diaphragm or vena cava. Resection using hepatic vascular isolation and hypothermic perfusion allows a longer ischaemic time of up to 147 min[4]. This technique is not applicable to the smaller child because of the need to cannulate the hepatic artery and portal vein. Resection using normovolaemic haemodilution anaesthesia involves intraoperative removal of the patient's blood and replacement with three times the volume of Ringer's lactate and reinfusing back blood after cessation of major blood loss. Hypothermia of 32°C and hypotension of 40–50 mmHg is maintained[5]. The technique reduces the need for massive intraoperative transfusion. The use of an extracorporeal oxygenator–warmer circuit and roller pump enables rapid transfusion to replace massive blood loss[6]. The two latter techniques do not, however, provide a bloodless field for resection.

The use of profound hypothermia and circulatory arrest to facilitate the removal of abdominal tumours invading the inferior vena cava was first described in 1978 in two children, one with a Wilms' tumour and the other with an adrenocortical carcinoma[7]. Ein *et al.* described a series of six children with malignant hepatic tumours in which resection was performed with cardiopulmonary bypass, profound hypothermia and circulatory arrest[1]. The technique allows an unhurried resection in a bloodless field. In a more recent series the same technique was used in resections of five hepatic and two intravascular Wilms' tumours. The adequacy of the resection margins were determined by immediate frozen sections and in two patients further resections were required[8].

In our patient the preoperative CT scan suggested that the tumour was closely involved with the inferior vena cava and would have been considered unresectable by conventional techniques. The use of cardiopulmonary bypass obviously adds an extra dimension in terms of potential serious complications. However, since adequate resection offers the only means of cure in paediatric liver malignancies[2], the added risks involved can be justified in selected cases if it offers the potential of complete resection. The technique has so far only been used in children. However, in selected circumstances, the technique could conceivably be applied to adults.

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Management of pancreatic pseudocysts

R. Andersson, M. Janzon, I. Sundberg and S. Bengmark

Department of Surgery, Lund University, S-22185, Lund, Sweden
Correspondence to;
Dr R. Andersson

Between 1969 and 1987, 68 patients with pancreatic pseudocysts were treated. The median cyst size was 10 cm (range 2–25 cm). Nine patients were managed conservatively with resolution of the pseudocyst occurring in eight patients. These patients had significantly smaller (median 4 cm) cysts compared with those in both percutaneously and surgically treated patients ($P<0\cdot01$). *In 22 patients the pseudocysts (median 9 cm) were punctured percutaneously under ultrasound guidance and the cyst fluid was aspirated or drained through a catheter. Complete resolution occurred in 13 patients after 1–4 (mean 1·8) punctures per patient, regression occurred in six patients after 1–4 (mean 2·0) puncture procedures per patient and three were unchanged. No complications were noted, except that two patients treated percutaneously required additional surgery. Thirty-seven patients were managed surgically (median cyst size 11 cm) with external drainage (12 patients), cystgastrostomy (17 patients), cystduodenostomy (three patients) cystjejunostomy (three patients) and pancreatic resection (two patients). Resolution of the cyst was noted in 29 patients, regression in five and three were unchanged. Five patients required additional surgery. Twelve complications were seen in ten patients (27 per cent), most frequently after external drainage. One patient died after surgical treatment. Mean hospital stay was 13 days among patients treated conservatively and 30 days in both percutaneously and surgically treated patients. Aspiration or catheter drainage of pseudocyst fluid guided by ultrasonography seems a safe and effective treatment of pancreatic pseudocysts and should be considered as initial therapy. If surgery is required cystgastrostomy is preferred.*

Keywords: Pancreatic pseudocyst, surgery, ultrasonography, percutaneous drainage

Treatment of pancreatic pseudocysts has traditionally been surgical[1–4], and surgical management has continued to dominate in the twentieth century[5,6]. However, during the last decade, the introduction and further development of diagnostic techniques such as ultrasonography and computed tomography have improved diagnosis and enabled the development of percutaneous aspiration or drainage of pancreatic cysts[7,8].

The present study was performed in order to evaluate our experience in the management of pancreatic pseudocysts.

Patients and methods

The records of 68 patients with pancreatic pseudocysts treated at the Department of Surgery, Lund University, between 1969 and 1987 were reviewed retrospectively Forty-seven patients (69 per cent) were men and 21 (31 per cent) were women. The mean age was 51 (range 19–95) years The predominant aetiological factor was chronic alcohol abuse (43 per cent), followed by blunt abdominal trauma (16 per cent), biliary tract disease (15 per cent) and cysts seen in association with pancreatic carcinoma (6 per cent) In 14 patients (21 per cent) no definite aetiology could be defined. Abdominal pain was present in 90 per cent of the patients on admission Thirty-two per cent of patients had a history of nausea or vomiting; a palpable mass was present in 12 per cent, weight loss in 10 per cent and jaundice was noted in 9 per cent. The mean serum amylase level was elevated (19·0 (4·0) μkat/l (mean and s.e.m.) normal range 1·2–5·0 μkat/l)

One patient required emergency treatment of the cyst owing to spontaneous rupture The pseudocysts arising after acute pancreatitis (24 patients) were in general initially managed conservatively in order to allow the cyst wall to mature before definitive treatment was decided

Ultrasonography, computed tomography and endoscopic retrograde cholangiopancreatography (ERCP) were introduced during the latter half of the study period, while angiography was used during the first half of the study (*Table 1*) The median cyst size (maximal diameter) in the whole series was 10 cm (range 2–25 cm) Conservative management was followed in nine patients, ultrasonically guided percutaneous needle aspiration or catheter drainage in 22 patients and surgical treatment in 37 patients There were no differences in aetiology or symptoms between the different groups, except that all four patients with underlying pancreatic carcinoma were treated surgically. After the introduction of the percutaneous technique, 47 per cent of patients with pancreatic pseudocysts have been treated with this method and during the last 4 years no patient has been assigned to primary surgery Conservatively managed patients had significantly smaller cysts compared with percutaneously or surgically treated pancreatic pseudocysts ($P<0\cdot01$) The difference in cyst size between patients treated percutaneously or surgically was not significant. In these two groups cysts that were less than 4 cm diameter were seen in patients with multiple cysts

Two or more cysts were seen in one conservatively managed, six percutaneously aspirated and five surgically treated patients Investigation showed communication with the main pancreatic duct in two, four and one patient respectively Cyst fluid was analysed for tumour cells and bacterial growth Tumour cells were found in cyst fluid from two operated patients Positive bacterial cultures were found in four percutaneously and two surgically treated patients

Conservative treatment (nine patients)

The median pseudocyst size was 4 cm (range 2·5–5 cm). Follow-up was with ultrasonography or computed tomography for a median of 5 months (range 1–78 months)

Percutaneous treatment guided by ultrasonography (22 *patients*)

The median cyst size in this group was 9 cm (range 2–15 cm). The site in the epigastrium with the shortest distance to the cyst was chosen, after which puncture was performed under sterile conditions. Eleven

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Table 1 *Diagnostic procedures in 68 patients, subdivided by the treatment group*

	Ultrasound	CT	Barium study	ERCP	Angiography
Conservative treatment ($n=9$)	8	6	—	2	1
Percutaneous treatment ($n=22$)	19	10	—	1	2
Surgical treatment ($n=37$)	7	5	14	7	7
Total ($n=68$)	34	21	14	10	10

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography

Table 2 *Results of treatment of pancreatic pseudocysts in 68 patients*

	Resolution	Regression	Unchanged
Conservative treatment ($n=9$)	8	—	1
Percutaneous treatment ($n=22$)	13	6	3
Surgical treatment ($n=37$)	29	5	3
Total ($n=68$)	50	11	7

Table 3 *Complications after surgical treatment of pancreatic pseudocysts*

	Internal drainage ($n=25$)	External drainage ($n=12$)	Total ($n=37$)
Fistula	3	4	7
Abscess	1	1	2
Bleeding	—	1	1
Wound rupture	—	1	1
Sepsis	—	1	1
Total	4	8*	12
No of complications per patient	0·16	0·67	0·32

* $P<0{\cdot}01$ compared with number of complications after internal drainage

patients had only one puncture procedure, six patients had two and five patients three or four punctures. Aspiration of cyst fluid was performed in 13 patients, in a mean of 1·7 puncture procedures per patient (range 1–4), and drainage through a small indwelling catheter was performed in nine patients, three of whom had an initial aspiration. The catheter was left in the cyst cavity for 1–7 days The mean amount of evacuated cyst fluid was 570 ml (range 10–5000 ml) The patients were then followed up with ultrasonography or computed tomography for a median of 5 months (range 1–18 months)

Surgical treatment (37 *patients*)

These patients had a median cyst size of 11 cm (range 3–25 cm) The surgical treatment consisted of external drainage in 12 patients, cystgastrostomy in 17, cystduodenostomy in three, cystjejunostomy in three and pancreatic resection in two patients. Surgically managed patients were followed up for a median of 6 months (range 1–84 months)

Statistics

Statistical analysis was performed with Fisher's exact test and the Mann–Whitney rank sum test

Results

Conservative management (Table 2)

Conservative management resulted in resolution (i.e complete disappearance) of the pancreatic pseudocysts in eight of nine patients (89 per cent in this group, 12 per cent of the whole series), two of whom had a temporary relapse. No complications were seen.

Ultrasonographically guided percutaneous aspiration or drainage (Table 2)

This was successful in 19 of 22 patients (86 per cent): complete resolution occurred in 13 patients after a mean of 1·8 punctures, and regression (i.e. non-complete disappearance) in six patients after a mean of 2·0 punctures. Two patients required additional surgical treatment (cystgastrostomy and external drainage respectively); in one of these two patients the cyst communicated with the main pancreatic duct. No other complications were noted after the percutaneous procedure. Indwelling drainage catheters were not associated with any side-effects.

Surgical treatment (Table 2)

Surgical treatment resulted in resolution of the pseudocyst in 29 patients and regression in five patients, while the cyst size remained unchanged in three patients. No difference in outcome after surgery could be stated when comparing pseudocysts arising after acute (eight patients) or chronic (11 patients) pancreatitis. Three patients required additional surgery for their pancreatic pseudocysts: two patients had a pancreatic resection, one of which was due to a pancreaticopleural fistula, and the third patient had external drainage. Two patients had gastroenteroanastomosis performed on the second occasion. The complications after surgical treatment are summarized in *Table 3*. Twelve complications occurred in ten patients (27 per cent). The most frequent (seven patients) complication was development of a fistula As can be seen, external drainage was associated with a high complication rate (eight complications in 12 patients; $P<0{\cdot}01$ compared with complications among patients with internal drainage). One patient with alcohol-induced chronic pancreatitis and a pancreatic pseudocyst, who was treated with surgical external drainage, died. He had a reoperation on the fourth postoperative day with a negative laparotomy because of suspected intestinal obstruction, developed a small bowel fistula, deteriorated and died after 2 weeks with multiple organ failure. The mortality rate among operated patients therefore was 2·7 per cent and the hospital mortality rate for the whole series was 1·5 per cent

Hospital stay

The mean hospital stay for conservatively treated patients was 13 days (range 1–40 days) and was 30 days for both percutaneously (range 4–70 days) and surgically (range 5–85 days) treated patients, reflecting the underlying disease and the patients condition rather than the treatment *per se.*

Discussion

Morbidity and mortality following surgical treatment of pancreatic pseudocysts is considerable and postoperative complication rates have been reported to be around 30 per cent[9–11], as in the present study. Our finding that external surgical drainage was associated with a high complication rate (eight out of 12 treated patients) is in accordance with previous work[6,12,13] In our material, internal drainage (in two-thirds performed as a cystgastrostomy) caused significantly fewer postoperative complications ($P<0{\cdot}01$) compared with surgical external drainage. With the advent of non-invasive diagnostic techniques the number of 'diagnostic' exploratory laparotomies soon after an acute pancreatitis attack diminished, an operation often resulting in external surgical drainage of the cyst. This partly explains the high morbidity following external drainage, as acute procedures are associated with a higher morbidity and mortality. Hence, internal and external surgical drainage has not been used in equivalent groups of patients. The outcome after surgery was similar in pseudocysts occurring after acute or chronic pancreatitis as previously reported[14]. In chronic uncomplicated and asymptomatic pseudocysts, a conservative approach is advocated.

Only one patient required acute surgical intervention owing to a cyst complication[15]. Subacute surgical intervention is associated with frequent postoperative complications[6,13,19] Instead, an initial conservative approach allows the cyst wall to mature, giving fewer complications after internal drainage, if surgery is needed[12]. It also allows lesser sac accumulations or intrapancreatic fluid collections to resolve spontaneously[16], leaving the true pancreatic pseudocysts for definitive treatment. Only half of acute 'cysts' will progress to chronic pseudocysts[17] In the present study, eight out of nine pancreatic pseudocysts treated conservatively resolved. Previous reports on successful conservative management emphasize that cysts less than 4 cm in diameter will resolve[11,18,19].

An alternative to surgical internal drainage is percutaneously performed cystgastrostomy with a double pigtail catheter inserted under gastroscopic and ultrasound guidance: it was successful in 19 out of 21 reported patients[20]. Percutaneous puncture or drainage of cyst fluid was successful in 19 of 22 treated patients in our study, while two required additional surgical treatment. Other studies on percutaneous puncture and drainage of pancreatic pseudocysts guided by ultrasonography have also been promising[7,8,21–23], with a high success rate even after a mean follow-up period of 2 years.

In conclusion, small pancreatic pseudocysts seem safe to manage conservatively as they frequently resolve and complications are rare. At least 10 per cent of pseudocysts, probably far more, can be treated thus; in the remaining patients, the cyst wall should be allowed to mature and then should be treated by percutaneous puncture and drainage. In those instances where surgical treatment is needed, internal drainage should be performed if possible.

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Extended role for needle biopsy in the management of carcinoma of the breast

Treatment choice in primary breast cancer is wide and still controversial; it seems likely that the optimum treatment for individual patients could be dictated by biological indicators of tumour behaviour. If biopsy could provide prognostic information as well as detailed tissue diagnosis then definitive treatment, with or without adjuvant systemic therapy, could be planned from the outset. We studied 140 patients with a clinical diagnosis of primary breast cancer to determine how much information could be obtained from Tru-Cut® needle biopsies performed at the first clinic visit. Ten patients were found to have benign disease. Of 130 carcinomas, 123 (95 per cent sensitivity) were diagnosed correctly from the needle biopsies, with seven false negative and no false positive results (100 per cent specificity). Precise histopathology was predicted in 121 (93 per cent). Grade was correctly assessed in 77 of 112 (69 per cent), but needle biopsy was not accurate for assessment of lymphatic invasion nor elastosis. Steroid hormone receptors were assayed in 59 needle biopsies, and the incidence of oestrogen receptor positivity (34, 58 per cent) was similar to the resected tumours (35, 59 per cent), but the incidence of progesterone receptor positivity (26, 44 per cent) was lower (33, 56 per cent, P < 0·04). Immunostaining with monoclonal antibody human milk fat globule membrane was accurate in the needle biopsies. DNA analysis by flow cytometry was performed in 37 tumours and the concordance between needle biopsies and resected samples was high. Tru-Cut needle biopsy obviates open biopsy and gives reliable detailed information.

Keywords: Breast cancer, needle biopsy, receptors, flow cytometry, monoclonal antibodies

A. D. Baildam,
L. Turnbull*,
A. Howell†,
D. M. Barnes‡ and
R. A. Sellwood

Departments of Surgery,
**Histopathology, †Medical*
Oncology and ‡Clinical Research,
The Christie Hospital, Wilmslow
Road, Manchester M20 9BX, UK
Correspondence to:
Mr A. D. Baildam, University
Hospital of South Manchester,
Nell Lane, West Didsbury,
Manchester M20 8LR, UK

Changes in the understanding of the biology of breast cancer have led to the use of conservation surgery and, in some centres, to the use of systemic treatment before operation[1,2]. It seems likely that optimum treatment for individual patients will be dictated increasingly by biological indicators of tumour behaviour. It is important that a biopsy should provide not only a detailed tissue diagnosis but also as much prognostic information as possible so that definitive treatment, with or without adjuvant systemic therapy, may be planned from the outset.

Early systemic therapy limits the time period during which the tumour can produce mutant clones, some of which may be resistant to endocrine manipulation or cytotoxic agents[3–8]. Theoretically, systemic treatment before operation could produce regression of the tumour to the extent that histopathological grade, receptor status, markers for differentiation and cell kinetics could all be altered or lost. Biopsy of the tumour before any treatment would be the only accurate opportunity for a detailed histological diagnosis and examination of other features.

In cancer of the breast a diagnosis made by histological examination is essential before treatment is started[9–14]. Tru-Cut® (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) needle biopsies for histological examination are quick and simple to carry out, and have been commended for diagnosis in cancer of the breast[9,10,12,15,16]. The aim of this study was to determine how much information of both diagnostic and prognostic value could be obtained from a Tru-Cut needle biopsy, compared with information obtained from the resected tumour taken at definitive operation. Four factors were examined: the histological features of the tumour, oestrogen and progesterone receptors (ER and PR), immunostaining with a monoclonal antibody against human milk fat globule membrane (HMFG-1), and DNA ploidy assessed by flow cytometry

Patients and methods

This prospective study was carried out on patients who presented to the breast clinic at the University Hospital of South Manchester, between 1 April 1984 and 1 April 1986, with a clinical diagnosis of primary operable carcinoma of the breast. Of the 140 patients originally entered, ten proved not to have carcinoma: 130 patients with primary carcinoma of the breast were available for study and their clinical characteristics are shown in *Table 1*. A Tru-Cut needle biopsy was taken when each patient was first seen in the clinic, and the operation was performed a median of 8 days later (range 5–14 days). Either wide local excision followed by radiotherapy (66 patients) or simple mastectomy (64 patients) was performed as deemed appropriate for each patient after consideration of tumour size. After excision a portion of tumour (approximately 70 mg) was stored in liquid nitrogen for estimation of receptors, and the remainder was placed in formalin for histopathology, immunostaining and flow cytometry

The Tru-Cut biopsy technique

Biopsies of tumour were taken after infiltration of the breast with local anaesthetic. Initially a stainless steel pistol was used to take the biopsies with the Tru-Cut needle, but because patients were disconcerted by its use the gun was abandoned after the first 21 biopsies[17].

Several cores were taken from each tumour. The maximum size of a core was $20 \times 1 \times 1$ mm³ Compression (usually 2–4 min) limited bleeding. Patients were advised to take simple analgesics if necessary Two cores were placed in 10 per cent buffered formalin for fixation and subsequent histopathological examination, immunostaining with monoclonal antibodies, and flow cytometry. Two cores were frozen and stored in liquid nitrogen for receptor analysis. Cytology smears were made from these cores for confirmation of malignancy.

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Histopathology

Sections of all primary tumours were processed routinely by a single pathology laboratory. Tissue was fixed for up to 48 h in buffered formalin, and subsequently embedded in paraffin wax on a tissue processor. Representative blocks were sectioned at 4 μm thickness and stained with haematoxylin and eosin. The slides of Tru-Cut biopsies and surgically removed samples were examined by a single pathologist (L.T.) in a coded and randomized order.

Receptor assays

Fifty-nine pairs of Tru-Cut biopsy specimens and resected samples were assayed for ER and PR by the isoelectric focusing technique, which has been described elsewhere[18,19]. Any positive value with an appropriate isoelectric point was taken to indicate a positive receptor value.

Immunostaining technique for HMFG-1

The monoclonal antibody HMFG-1 was raised in mice as described by Taylor-Papadimitriou and colleagues, and was a gift from them[20]. The details of preparation and immunostaining have been described[21]. At the initial assessment using a microscope at low power, the distribution of tumour cells was examined and any gross variations in staining intensity were noted. Intensity was recorded but, as it is difficult to quantify objectively, it was not used in the final analysis.

Each section had a minimum of 400 tumour cells counted and assessed for the presence of stain. The site of staining was noted as being cytoplasmic, on the cell membrane, or a combination of both. In some tumours staining was found outside the cells in extracellular deposits. This was expressed as the number of deposits seen per high power (400 ×) field. All slides were assessed by one observer (A.D.B.).

DNA ploidy by flow cytometry

Tumours from 37 patients were analysed by flow cytometry. They were selected purely on the basis that the paired tissue blocks were available at the time of this part of the study. Paraffin-embedded, formalin-fixed material was used throughout. Nuclear suspensions for flow cytometry analysis were prepared by the method of Hedley, but with a slight modification of the fluorochrome[22]. Measurements were obtained from a Cytofluorograph Model 4800A (Biophysics System Incorporated, Mahopac, New Jersey, USA) with an argon laser interfaced to a Hewlett-Packard 9845A Desk Top Computer (Hewlett-Packard, UK). Five thousand nuclear particles were measured from each sample.

Half peak coefficient of variability was evaluated for each histogram and ranged from 2 to 10 per cent (median 5 per cent). For the description of aneuploid peaks, DNA indices were calculated as the ratio of the aneuploid peak channel to the first peak that was considered to be diploid or nearly diploid and that was present on each histogram. In multiploid tumours each peak was defined by its own DNA index and the greatest one used for the overall analysis[23]. For calibration of the cytofluorograph, normal human peripheral blood lymphocytes fixed in 95 per cent ethanol and paraffin-embedded tonsils were used. These gave comparable fluorescence for diploid histograms.

Table 1 *Clinical characteristics of patients*

Number of patients	130
Age (years)	
Mean	60
Median	60
Range	33–84
Premenopausal	35 (27)
Perimenopausal	5 (4)
Postmenopausal*	90 (69)
Tumour size (cm)	
Mean	3·2
Median	2·7
T stage	
T_1	31 (24)
T_2	72 (55)
T_3	21 (16)
T_4	6 (5)
N stage	
N_0	98 (75)
N_1	32 (25)
Surgery	
Wide local excision	66 (51)
Simple mastectomy	64 (49)

*Postmenopausal was defined as a minimum of 2 years since the last menstrual period, values in parentheses are percentages

Statistical analysis

A χ^2 analysis and Fisher's exact test were used for each comparison to relate frequencies of integers between two variables. In accordance with convention $P \leqslant 0·05$ was taken to be significant. Comparisons between two variables recorded as actual numbers (e.g. ER value with staining of extracellular deposits) were made with the Mann–Whitney *U* test, Pearson's correlation and Kendall's non-parametric correlation. Wilcoxon's matched pairs test was used for comparison of the Tru-Cut biopsy with the resected sample when indicated. Eighty variables from each patient were analysed by means of a Hewlett-Packard 9845A desk top computer with a database and statistics program.

Results

Histopathology

Of a total of 140 pairs of Tru-Cut biopsies and resected samples, 130 tumours were malignant. Of these 123 were diagnosed correctly on the Tru-Cut biopsy sample, which gave a sensitivity of 95 per cent. No Tru-Cut biopsy was reported as malignant which subsequently was found to be benign; the specificity therefore was 100 per cent. The accuracy of biopsy did not depend on the size of tumour (*Table 2*).

The definitive histological diagnosis was obtained from 131 (94 per cent) of the Tru-Cut biopsies, and the correlation between the Tru-Cut and definitive surgical pathology was high (*Table 3*). Of the seven tumours incorrectly diagnosed as benign on the needle biopsies, six were found to be infiltrating duct carcinoma and one was an infiltrating lobular carcinoma. Four Tru-Cut biopsies showed intraduct carcinoma only, in two of these this was the final diagnosis, and in two infiltrating duct carcinoma was found in addition. There was adequate tissue on Tru-Cut biopsies to grade 99 of 104 (95 per cent) of the infiltrating duct carcinomas compared with 110 of 112 (98 per cent) in the case of the surgically resected tumours, but the grades of each pair of tumour samples did not always agree. In 77 of 104 (74 per cent) samples the grades were identical, in 14 (13 per cent) the grade was lower in the resected tumour, and in eight (8 per cent) it was higher (*Table 4*), but these differences were not significant.

It was possible to decide on the presence or absence of lymphatic invasion in 103 of 130 (79 per cent) of the Tru-Cut

Table 2 *Size of tumour and accuracy of needle biopsy*

		Tumour size (cm)				
Accuracy of Tru-Cut biopsy	*n*	0·5–1·0	1·1–2·0	2·1–3·0	3·1–5·0	≥5·1
Accurate						
Malignant	123	6	33	41	27	16
Benign	10	4	3	1	2	0
Inaccurate						
Malignant (false negatives)	7	1	2	4	0	0

Fisher's exact test: no significant differences were found

Table 3 *Comparison of histopathology from needle biopsies with that from resected tumours*

Pathology on needle biopsy	Pathology on resected tumour				
	IDC	ILC	Benign	Mucoid	Intraduct
IDC	104				
ILC		12			
Benign	6	1	10		
Mucoid				3	
Intraduct	2				2

IDC, infiltrating duct carcinoma; ILC, infiltrating lobular carcinoma; no significant differences were found

Table 4 *Comparison of grades obtained from needle biopsy and resected tumour*

Grade on needle biopsy	Grade on resected tumour			
	I	II	III	NG
I	9	1		
II	2	41	7	1
III	1	11	26	
NG	2	7	3	1

NG, not possible to grade; no significant differences were found

Table 5 *Oestrogen and progesterone receptor assays: comparison of sample weights and cytosol protein concentrations*

	Sample weight (mg)		Cytosol protein (mg)	
	Tru-Cut biopsy	Resected tumour	Tru-Cut biopsy	Resected tumour
Mean (s.d.)	26·7 (9·3)	67·5 (14·9)	3·3 (2·1)	6·4 (2·6)
Median	25·0	70·0	2·7	6·2
Range	25–30	30–100	0·3–12·3	2·2–14·2

samples, and in 114 of 130 (88 per cent) of the resected tumours. This difference was not significant. Lymphatic invasion was noted in 12 (11 per cent) and in 32 (29 per cent) samples respectively, and this difference was significant ($\chi^2 = 9\cdot03$, $P < 0\cdot002$).

Elastosis could be assessed in 97 (75 per cent) of the Tru-Cut biopsies and 110 (85 per cent) of the resected tumours: 26 (27 per cent) and 41 (37 per cent) respectively of each group demonstrated elastosis, and this difference was significant ($\chi^2 = 4\cdot29$, $P < 0\cdot05$).

Receptor analysis

Reliable receptor analyses were available on 59 of 61 Tru-Cut biopsies (97 per cent); in two (3 per cent) biopsies the results were unreliable because of low concentrations of cytosol protein. The median weight of the resected samples was just more than twice that of the Tru-Cut biopsies, and there were correspondingly higher concentrations of cytosol protein in the resected tumours (*Table 5*)

The proportion of ER-positive tumours was similar in the needle biopsies and resected samples of tumour (58 per cent in Tru-Cut biopsies, 59 per cent in resected tumours). The mean value for ER was greater in the resected tumours than in the Tru-Cut biopsies, but the difference was not significant (*Table 6*).

The proportion of PR-positive tumours was significantly higher in the resected tumours (56 per cent) compared with the Tru-Cut biopsies (44 per cent: $\chi^2 = 4\cdot37$, $P < 0\cdot04$; *Table 6*) The mean concentration of PR in the resected tumours (65·2 fmol/mg cystol protein) was greater than that in the Tru-Cut biopsies (53·1 fmol/mg cystol protein), but this did not achieve significance.

Immunostaining with HMFG-1

Of 130 Tru-Cut biopsies, 121 (93 per cent) contained sufficient malignant tissue for an assessment of HMFG-1 staining (*Table 7*). A sample of 47 sections was assessed on two occasions 3 months apart to determine the degree of discordance in interpretation. In 40 of 47 (86 per cent) the assessment of the percentage of cells stained was within 10 per cent of the value found on the first occasion. In the tumours which had been assessed as positive staining of extracellular deposits on the first reading, all were assessed as positive on the second occasion, but there were minor differences in the number of deposits counted.

The results of immunostaining in the resected tumours were compared with those from the Tru-Cut biopsies by Wilcoxon's paired *t* test and linear regression analysis and significant correlations were obtained. But there was a trend for the percentage of cells which stained to be lower in the Tru-Cut biopsy than in the resected tumour (*Table 7*).

Extracellular staining was more apparent in the resected tumours than in Tru-Cut biopsies. Of the 130 tumours, 21 (16 per cent) were found to have staining of extracellular deposits in the Tru-Cut biopsy specimen, compared with 40 (31 per cent) in the resected tumour ($\chi^2 = 6.94$, $P < 0\cdot01$). Extracellular deposits were recorded in only one Tru-Cut

Table 6 *Receptor status and concentrations in 59 tumours*

	Tru-Cut biopsy	Resected sample	*P*
ER + ve	34 (58%)	35 (59%)	n.s
ER value (fmol/mg cystol protein)			
Mean (s.d.)	62·0 (88·1)	166·8 (260·1)	n s
Median	33·0	54·0	
Range	3–460	6–1258	
PR + ve	26 (44%)	33 (56%)	<0·04*
PR value (fmol/mg cystol protein)			
Mean (s.d)	53·1 (44·9)	65·2 (81·4)	n.s
Median	39·0	30·0	
Range	7–229	3–300	

ER, oestrogen receptor, PR, progesterone receptor, *$\chi^2 = 4\cdot370$ (Tru-Cut biopsy *versus* resected sample)

Table 7 *Human milk fat globule membrane immunostaining: comparison of cells stained in Tru-Cut biopsies with those from resected tumours*

Human milk fat globule immunostaining	All patients ($n = 130$)		
	Tru-Cut biopsy	Resected tumour	*P*
Percentage of cells stained			
NG	9 (7%)	1 (1%)	
Nil	32 (25%)	23 (18%)	
1–9	21 (16%)	21 (16%)	
10–29	25 (19%)	25 (19%)	
30–49	15 (11%)	19 (15%)	
50–100	28 (22%)	41 (31%)	
			n s.
Mean (s d) (%)	22 (26)	31 (29)	n s
Median (%)	10	14	
Range (%)	0–83	0–92	
Cell membrane + ve	42 (32%)	39 (30%)	n s.
Extracellular deposits + ve	21 (16%)	40 (31%)	<0·01*

NG, not possible to gauge; *$\chi^2 = 6\cdot94$, Tru-Cut biopsy *versus* resected tumour

Table 8 *Comparison of DNA ploidy analysis by flow cytometry*

	Tru-Cut samples ($n = 37$)	Resected samples ($n = 37$)
Diploid tumours	10 (27)	9 (24)
Tetraploid and near-tetraploid tumours*	17 (46)	16 (43)
Other DNA aneuploid†	11 (30)	11 (30)

Values in parentheses are percentages; *DNA index 1·8–2·0; †DNA index 1·2–1·7 and ≥2·1

sample when the definitive tumour did not reveal extracellular staining.

DNA ploidy by flow cytometry

The findings in the resected tumour were essentially similar to those in the Tru-Cut biopsies (*Table 8*). The number of nuclear particles in the G2/M phase or in the second major peak in each Tru-Cut biopsy was compared with the number in that same peak from the analysis of resected tumour. There were some minor differences. One diploid tumour was tetraploid in the second sample (taken as 'G2/M' > 10 per cent of total cell population), and there were minor changes in 'other DNA-aneuploid' tumours. When tetraploid tumours were considered, there were apparent differences between the Tru-Cut biopsies and the resected tumours. In six tumours the number of particles in the tetraploid peak was greater, in four it was lower, and in five it was the same. These differences failed to achieve statistical significance.

Discussion

Optimum treatment for carcinoma of the breast is still the subject of considerable debate. Although there has been a trend towards minimal surgery it is by no means clear that this is the treatment of choice for all patients; neither is it certain which patients should receive systemic treatment as part of initial management of the primary disease. It seems likely that as molecular biology is used to develop probes and immunology to develop tumour markers, it will become apparent that the treatment of choice for individual patients may need to be tailored to each specific type and prognostic group of tumour. The need to define precise pathology and predict the likely behaviour of a tumour before definitive treatment is planned is therefore of increasing importance.

Open biopsy, with or without frozen section examination, is inefficient in terms of time taken by surgeons, anaesthetists and pathologists[9,24,25], and it may require admission and general anaesthesia. An alternative is to take a small sample of tumour in the outpatient clinic with a drill or needle. High speed air drills produce good cores of tissue which result in high diagnostic accuracy and no false-positive results, but the equipment is cumbersome and the noise of operation disturbing to patients[26,27].

Fine needle aspiration and cytological examination has been used extensively[28]. It is cheap, easy to perform and virtually free from complications[29]. Unfortunately false positive results occur[10,15,30–33]. In particular there are difficulties in the interpretation of cells from some benign proliferative disorders[11]. Other studies confirm the significant false positive rate that can occur with cytology alone[34–37].

The advantages of Tru-Cut biopsy for the patient with operable disease are clear; it has high sensitivity, it is accurate in assessing pathology, and considerable information may be obtained in addition to a simple diagnosis. The sensitivity of the technique was 95 per cent. This compares favourably with results reported by previous workers who found sensitivities of 89 per cent[12], 80 per cent[16], 79 per cent[32], 67 per cent[9], 74 per cent[10] and 79 per cent[33]. There was no false positive result either in this study or in previous studies. Tru-Cut needle biopsy did not provide sufficient tissue for accurate assessment of lymphatic or vascular invasion or elastosis, and both were underestimated, but these factors are relatively unimportant in the prediction of prognosis. This suggests that there is not a sufficiently representative sample to compensate for tumour heterogeneity for these factors.

The Tru-Cut biopsy provided adequate tissue for receptor estimations by isoelectric focusing and the percentages of ER-positive and PR-positive tumours were consistent with those in other reported series[38–45]. The proportion of tumours which were PR positive in the resected specimens was significantly greater than that in the needle biopsies. This may be a reflection of heterogeneity of the tumours, or of technical difficulties in the assay when applied to small needle biopsy specimens. Receptor status has been reported to vary in different parts of the same tumour[46–49], and it seems inevitable that receptors will be found more easily in relatively large samples. The sensitivity of the isoelectric focusing technique depends on the total cytosol protein in the tissue[19]. Consistently lower protein concentrations were found in the Tru-Cut biopsies than in the resected tumours.

The results of this study indicate that ER and PR concentrations can be measured on needle biopsies: it should be possible to determine responsiveness more accurately by the use of needle biopsies both before and after tamoxifen[50]. The availability of monoclonal antibodies to ERs and PRs is likely to facilitate receptor estimations considerably.

Human milk is rich in antigens normally associated with the cell surface, and it provides an excellent medium for the production of antibodies to these constituents. The antibody HMFG-1 identifies antigens found on the milk fat globule membrane, and those present on the surface of normal mammary epithelium and within the ducts[21,51–53]. Mammary carcinomas express these antigens on the cell membrane, in the cytoplasm, and sometimes extracellularly. The pattern and intensity of staining varies greatly between one tumour and another and sometimes within different areas of the same tumour[53]. This makes objective assessment difficult. Various methods of assessment, including scoring systems, have been used, and prognostic information has resulted[21,52,54–56]. Only six of 130 (5 per cent) Tru-Cut samples provided insufficient material for HMFG-1 assessment. From the majority of Tru-Cut biopsies, the percentage of cells stained was an accurate reflection of the resected tumour. The Tru-Cut biopsy samples were adequate for the assessment of cell membrane staining but they were not adequate for the assessment of extracellular stain. This failure to detect extracellular deposits was significant.

Flow cytometry is a rapid and reproducible technique for determination of the DNA content of cells. The introduction of a method whereby paraffin-embedded tumours may be used for flow cytometric analysis has led to the examination of archival material, and a means by which cellular DNA content can be related to subsequent response to treatment, survival and a variety of other factors[22,23,57–59]. In one study aneuploid tumours recurred more rapidly than diploid tumours[60], and survival of patients after relapse may be related to DNA ploidy[61]. Aneuploidy has been associated with lymph node metastases[62], but others have failed to confirm the relationship[63,64]. Tru-Cut biopsy samples provided adequate tissue for DNA ploidy analysis by flow cytometry and it was not difficult to obtain 5000 nuclear particles after dissociation of the tissue. Histograms were consistent with those from resected tumours. In previous studies variations in DNA ploidy were not found between primary tumours and axillary metastases[58,64], were found rarely when multiple biopsies were taken in one study[65], and in another study they were found in two of eight tumours[66].

In summary in this study we found that it was possible to obtain almost as much information concerning a tumour from the needle biopsy as from the resected tumour. The advantages of Tru-Cut needle biopsy for the patient with operable disease are clear. It can be performed in the clinic at the first visit with the minimum of disturbance for the patient, and requires no specialized equipment or staff. What is important, and what cannot be quantified, is the experience of the individual who takes the biopsy and the experience of the histopathologist who interprets the tissue. A recent study found that needle biopsy or aspiration cytology is used to make the initial diagnosis in only 2–10 per cent of all new breast cancer cases[67]. One possible reason for the reluctance of clinicians to use needle biopsy techniques is the worry that malignant cells may be disseminated by the insertion of the Tru-Cut needle If this actually does occur, it does not seem to influence survival any differently from excision biopsy[68]. This study confirms and extends the value of Tru-Cut needle biopsy in the management of cancer of the breast.

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Omental transposition in the treatment of locally advanced and recurrent breast cancer

R. J. L. Williams,
I. J. C. Fryatt*,
W. C. Abbott†, and
H. White

Departments of Surgery and
**Computing, The Royal Marsden*
Hospital, Fulham Road,
London SW3 6JJ, UK
Correspondence to:
Mr H. White

An analysis was carried out of 43 patients treated by omental transposition for locoregional problems associated with breast cancer. Indications for surgery included advanced primary tumour (five), locally recurrent tumour (32), radiation induced sarcoma (two), and radionecrosis (four). Tumours were typically extensive (mean diameter 7·2 cm) and skin ulceration affected 30 patients. Other treatment modalities had been exhausted. Surgical excision followed by reconstruction using transposed omentum resulted in worthwhile local control and symptom relief in 31 patients (median duration 22 months). Chest wall disease rapidly recurred peripheral to the omental graft in 12 patients. On multiple regression analysis, duration of local control was significantly related to tumour diameter, ulceration, and earlier radioresistance (hazard ratios 15·8, 3·8 and 14·8 respectively). Survival (median 21, range from 1·5 to 122 months) correlated with tumour size, previous chemotherapy, and early re-recurrence (hazard ratios 7·2, 3·0 and 4·3). Omental transfer is a reliable method of restoring epithelial cover after radical surgery and is particularly useful after previous irradiation injury. In advanced and recurrent breast cancer, an aggressive surgical approach significantly improved the quality of life of most patients, but careful case selection is required to avoid inappropriate surgery for irremediable tumours.

Keywords: Omentum, breast neoplasms, radiation injuries, prognosis, local recurrence, survival

Despite changing public awareness, a number of women continue to present with locally advanced breast cancer Extensive locoregional recurrence occurs occasionally in the absence of overt distant metastases. Both may prove resistant to non-operative treatment: relentless tumour growth results in ulceration of overlying skin and secondary infection. Initial distress is compounded by that associated with a fungating and malodorous tumour mass.

Primary breast cancer is now commonly treated by a combination of local tumour excision and irradiation. Problems that may follow radical radiotherapy include tumour recurrence in the irradiated breast, radionecrosis and radiation-induced sarcoma.

While surgery for limited primary disease has become more conservative, attitudes to chest wall recurrence have also changed. Radical excision followed by reconstruction using myocutaneous flaps has become accepted practice in a number of centres[1]. However, poor vascularity in irradiated tissues, necrosis, and uncontrolled secondary infection may all be obstacles to wound healing. In such circumstances, the technique of omental transposition may offer advantages[2]. Transferred on a reliable vascular pedicle, greater omentum can be readily moulded to fit the extensive irregular crater that adequate cancer clearance creates. When required, it can be placed over synthetic mesh following full-thickness thoracic wall resection. The profuse granulation tissue which rapidly appears on the surface of exposed omentum provides an excellent base for skin grafting[3,4].

This report summarizes the results of omental transposition, the preferred technique of one surgeon (H.W.), undertaken in 43 patients for difficult problems relating to breast cancer and its treatment.

Patients and methods

Between the years 1977 and 1987, 43 women underwent omental transposition for breast cancer and related chest wall problems Mean age was 54 years (range 30–80 years). The indications for surgery were advanced primary breast cancer (five), recurrent breast cancer (32), radiation induced sarcoma (two), and radionecrosis (four)

Many patients had relatively slowly progressing tumours, and the interval between the initial diagnosis of cancer and omental transposition ranged from 14 months to 22 years (mean 72 months). Local disease was for the most part extensive. tumour diameter varied between 2 and 25 cm (mean 7·2 cm). In 30 patients with skin breakdown, ulceration had been present for up to 3 years (mean 13 months) Satellite cutaneous deposits of tumour were visible peripheral to the main lesion in 14 patients, and in three there was tumour in the contralateral breast Enlarged lymph nodes were palpable in ten patients, and six were known to have distant metastases at the time of surgery

Patients were typically referred for salvage surgery by colleagues in radiotherapy and oncology only after exhaustion of other therapeutic modalities All patients had at some time been irradiated, and 11 (26 per cent) received multiple courses to the breast and/or chest wall In 18, radiotherapy (mean 58 Gy, range 40–65 Gy) was given without tumour excision: 15 of this group presented with locally advanced primaries. Twenty-one patients had previously received cytotoxic chemotherapy (in two this was adjuvant to initial surgery). Thirty-six patients experienced one or more forms of endocrine manipulation. Assessable responses to earlier non-surgical treatments are shown in *Table 1*.

Preoperative assessment

The technical aspects of omental transposition to the chest wall are described and illustrated in detail elsewhere[4,5]

Briefly, extensive peritoneal adhesions or previous gastric or colonic resection were regarded as contraindications to attempting omental transfer Up-to-date assessment of the extent of malignant disease was considered essential Diagnosis was established by preoperative needle aspiration cytology or Tru-cut* (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) biopsy Where appropriate, computerized tomographic scanning was used to estimate the depth of chest wall infiltration While age itself was not a contraindication,

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† *Present address Surgical Associates, P.A., 711 Encino Place N E, Albuquerque, New Mexico 87102, USA*

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Table 1 *Assessable responses to other therapeutic modalities used before surgical referral*

Treatment	No of patients	CR	PR	Overall response (%)	Mean duration (months)
Radiotherapy	16	7	6	81	39
Chemotherapy	17	1	4	29	22
Further chemotherapy	9	0	1	11	
Endocrine therapy	29	6	2	28	27

CR, complete response, PR, partial response

Table 2 *Complications following omental transposition*

Complication	No. of patients
Omental necrosis (partial)	10
Incisional hernia	6
Wound sinus ± infection	4
Thromboembolism	4
Pulmonary collapse ± consolidation	4
Haemorrhage ± haematoma	2
Cardiac arrhythmia	2
Pneumothorax	1
Colonic devascularization	1

respiratory function tests were performed where surgical clearance might necessitate resection of one or more ribs or sternum.

Patients were given a detailed explanation of the likely postoperative course of events and possible complications It was emphasized that intended surgery was for control of local symptoms, and the procedure should not necessarily be regarded as curative.

Surgical technique

A plastic drape was used as a flap to separate the contaminated breast region from the abdominal operative field and the abdomen was explored through an upper midline incision. Abdominal access was used to remove both ovaries in five premenopausal women. Hepatic metastases were considered a contraindication to proceeding further in one patient

The omentum was first detached from the transverse colon along the embryological line of fusion and then freed from the greater curvature of stomach. Gastric branches of the gastroepiploic vessels were individually ligated, taking care not to occlude the gastroepiploic arcade itself. Absorbable ligatures were always applied to the omentum After careful assessment of the vascular contribution of each, either the left or the right gastroepiploic pedicle was divided at its origin. A right sided pedicle supplied the graft in 30 patients, while the left vessels were used on 13 occasions. Although a separate subcostal incision was used initially in this series, subsequently, the mobilized omentum was brought out of the abdomen through the upper part of the laparotomy wound. Care was taken to avoid torsion or traction of the vascular pedicle.

Every effort was made to excise all grossly neoplastic and infected tissue with at least a 2 cm margin. Surgery included mastectomy in 25 patients, underlying muscle was excised in 19, and a part of the thoracic cage was resected in eight. Attempted 'curative' resection in one patient involved a forequarter amputation. The omentum was tunnelled subcutaneously and sutured to the margins of the surgical defect. Both the tunnel and the exit from the abdomen were of sufficient width to avoid compression of the omental pedicle, even at the risk of a subsequent incisional hernia The chest wall was stabilized and intrathoracic structures protected by inserting prosthetic mesh (Marlex®, C.R Bard Incorporated, Massachusetts, USA) deep to the transposed omentum in six patients To allow for the development of granulation tissue and possible appearance of areas of partial necrosis, skin grafting was initially delayed for 10 to 14 days A 1.3 meshed split-thickness graft is now applied immediately, thereby considerably shortening inpatient stay.

When possible, patients were followed up at 3-monthly intervals after discharge from hospital Mortality, additional treatment and timing and distribution of further malignant disease were documented.

Analysis

Results were compiled retrospectively using the Clinical Research System at the Royal Marsden Hospital. Kaplan–Meier type curves of local control and survival after omental transposition were constructed The prognostic significance of each of a number of preoperative and operative factors was analysed using the log rank test (see results). To assess the importance of these factors independent of one another, Cox's multiple regression analyses were performed^6

Results

Restoration of epithelial cover was achieved in 39 patients. Duration of hospital inpatient stay ranged from 11 to 66 days, with a mean of 33 days.

Complications

Most of the complications affecting the omental flap were temporary and easily corrected (*Table 2*) Omental haematoma and venous thrombosis occasionally resulted in partial graft necrosis: this was easily débrided One patient was excluded from this series as intended omental transposition had to be abandoned when the left gastroepiploic vessels proved to be inadequate, resulting in total graft necrosis; transfer in subsequent cases was always based on a right sided pedicle. A devascularization injury to the transverse colon was the result of technical error in failing to recognize the plane separating the omentum and mesocolon. Segmental resection with primary colonic anastomosis was performed without further complication. Two patients later required repair of their subcostal hernias. No subsequent problem relating to intra-abdominal sepsis or adhesions was experienced. After chest wall excision and mesh repair, respiratory embarrassment was transient.

Lymphoedema of the upper limb was present at the outset in nine patients. This deteriorated in three cases and developed *de novo* in a further four. No improvement in swelling was seen as a result of omental transposition.

Local control

Removal of the main source of symptoms gave worthwhile palliation in 31 patients (median duration 22 months, range 2·5 months–10 years). Surgical reconstruction proved successful in the four patients treated for radionecrosis and none developed recurrent ulceration.

Omental transposition was combined with tumour excision in 39 patients. Further local recurrence occurred in skin surrounding the omental graft in 23 of these, and went on to involve the omentum in 13 Tumour confined to the transposed omentum was seen only twice. Recurrent chest wall disease again led to symptoms in 15 patients. Surgery had been of little or no benefit in 12 of this symptomatic group as the further recurrence became apparent within 2 months (*Figure 1*).

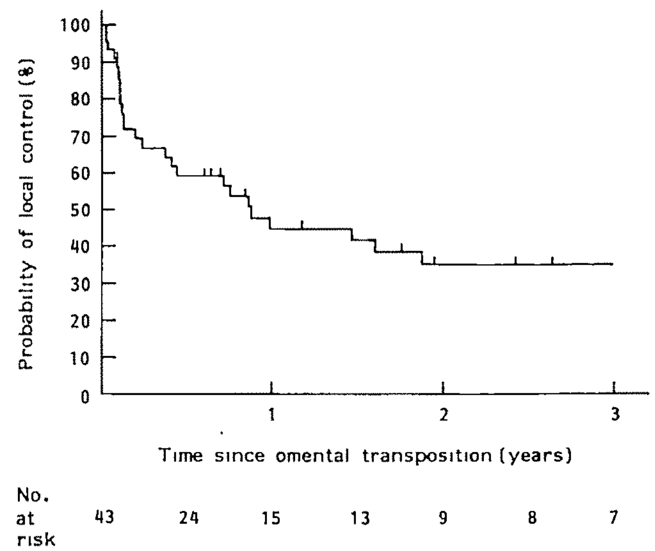


Figure 1 *Duration of local control after omental transposition (total number of patients, 43) Vertical bars indicate duration of follow-up*

Table 3 *Univariate analysis of local control and survival after tumour excision and omental transposition in 39 patients*

	Local control		Survival	
Variable	χ^2	*P*	χ^2	*P*
Tumour diameter (<5 cm, 5–10 cm, >10 cm)	16·38	<0 005	21 39	<0 005
Area of ulceration (0, $<20\,cm^2$, $\geqslant 20\,cm^2$)	9·19	<0·025	4 75	n.s.
Radioresistance	4·76	<0·05	2·71	<0·1
Interval from cancer diagnosis (<3 years)	7·08	<0 01	0 53	n.s
Previous chemotherapy	2·61	n.s.	5·79	<0 025
Satellite cutaneous deposits	5 68	<0·025	1 23	n s.
Lymph node enlargement	7·53	<0 01	0·70	n.s
Recurrence within 2 months of omental transposition			21 70	<0 005

n.s., Not significant

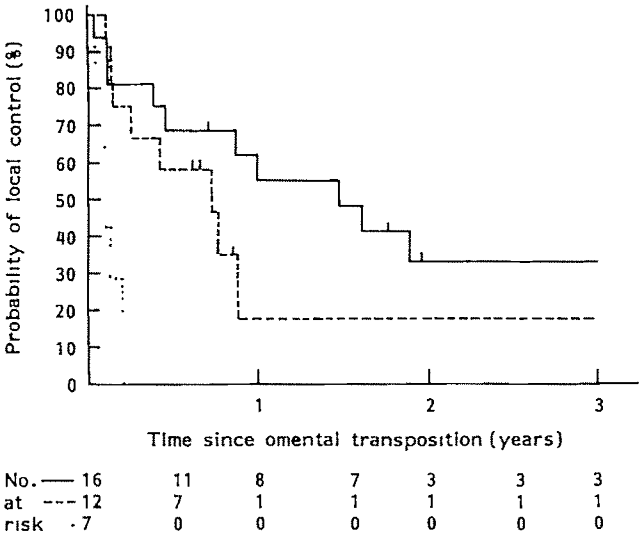


Figure 2 *Local control related to tumour diameter (total number of patients, 35); ——— <5 cm (16); – – – – – 5–10 cm (12), · · · >10 cm (7);* P<0 005 *Vertical bars indicate duration of follow-up*

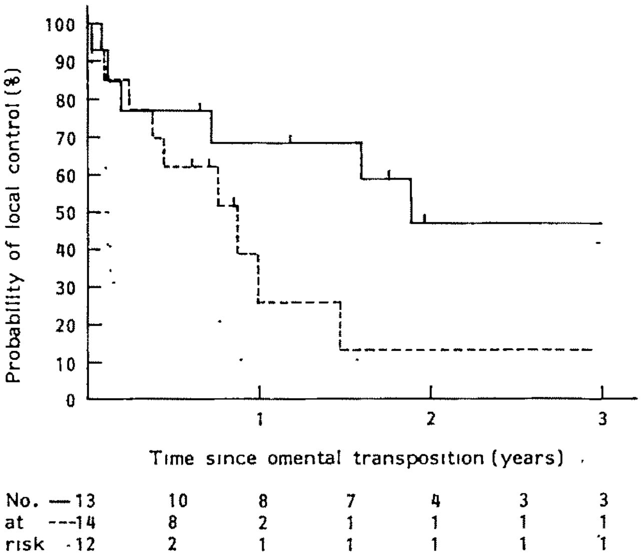


Figure 3 *Local control related to ulceration (total number of patients, 39); ——— no ulceration (13); – – – – – ulcer $<20\,cm^2$ (14), · · · · ulcer $\geqslant 20\,cm^2$ (12);* P<0·025 *Vertical bars indicate duration of follow-up*

Table 4 *Cox's multiple regression analysis of local control and survival after tumour excision and omental transposition in 39 patients*

	HR	*P*
Local control		
Tumour diameter (>10 cm)	15·8 (3·9–63 6)	≪0 001
Ulceration	3 8 (1·2–12·1)	<0 005
Radioresistance	14·8 (1·6–137)	<0 02
Interval from cancer diagnosis (<3 years)	2·2 (0·78–6 3)	<0·1
Survival		
Tumour diameter (>10 cm)	7 2 (1·7–31·3)	<0·001
Previous chemotherapy	3·0 (1·1–8 6)	<0·01
Recurrence within 2 months of omental transposition	4 3 (1·5–13·0)	<0·005

HR, hazard ratio, values in parenthesis are 95% confidence intervals

Local control was significantly shorter in patients with the following six features (*Table 3*): bigger tumours, particularly those in which the diameter exceeded 10 cm (*Figure 2*), ulceration (*Figure 3*), satellite cutaneous deposits, palpable lymph nodes, previous resistance to radiotherapy and a cancer history of less than 3 years. On multiple regression analysis, the variables which had independent influence were tumour diameter greater than 10 cm, ulceration, and radioresistance; the time interval between breast cancer diagnosis and omental transposition was of borderline importance (hazard ratios 15·8, 3·8, 14·8 and 2·2 respectively; *Table 4*).

Primary tumour grade and oestrogen receptor level were not available in most cases There was no significant association between local control and age, menopausal status, primary tumour size, response to endocrine therapy, known distant metastases, the extent of chest wall resection or histological confirmation of tumour clearance. However, detailed information on microscopic clearance at resection margins was available for only 20 of the 39 patients: 'complete' excision in 12, margin involvement in eight.

Survival

Overall survival after omental transposition ranged from 6 weeks to 10 years, median 21 months (*Figure 4*). Nineteen patients are alive at the time of writing, but only eight are free

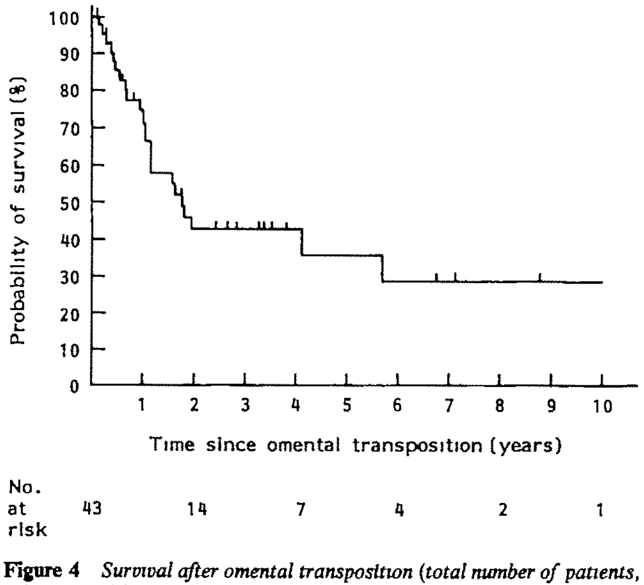
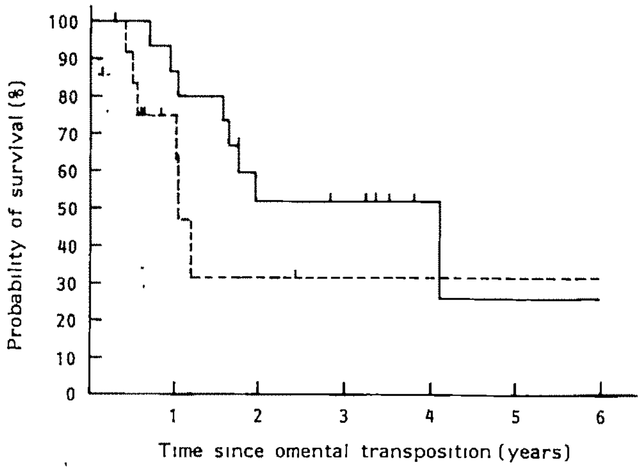


Figure 4 *Survival after omental transposition (total number of patients, 43). Vertical bars indicate duration of follow-up*



No. —— 16	13	7	6	2	1	1
at - - -12	6	2	1	1	1	1
risk ·7	1	0	0	0	0	0

Figure 5 *Survival related to tumour diameter (total number of patients, 35),* ——— *<5 cm (16),* - - - - - *5–10 cm (12),* ··· · *>10 cm (7),* P<0 005. *Vertical bars indicate duration of follow-up*

of malignant disease. Prognosis was closely related to tumour diameter, as measured in the resected specimen (*Figure 5*) Median survival was only 12 months in patients who had previously received cytotoxic chemotherapy (*Figure 6*) These factors were independent of one another on multiple regression analysis (hazard ratios 7·2 and 3·0 respectively; *Table 4*). Survival was further shortened in the patients who developed early local recurrence (hazard ratio 4 3).

Deaths have all been the result of either locally advanced or metastatic malignant disease Five of six patients who had disseminated breast cancer at the time of surgery together with four additional patients succumbed to distant metastases. Two patients had both metastases and extensive chest wall disease at the time of death In the patients who developed early recurrence, all ten deaths were related to breast cancer involvement of the chest and chest wall. Three further patients died of disease mainly confined to the thoracic region

Discussion

Most patients who develop locally advanced breast cancer or recurrence after mastectomy have associated distant metastases or develop them within a relatively short time Breast cancers are usually radiosensitive and aggressive radiotherapy is probably the treatment of choice[7]. Many cases then succumb to metastatic disease before their local disease again becomes apparent or troublesome. The reported incidence of further recurrence after radiotherapy ranges from 32 to 65 per cent[7–11]. Earlier treatment usually precludes the use of additional external beam irradiation within the same field, although a radioactive implant can occasionally be considered While responses to endocrine therapy are generally superior both in quality and duration to those obtained from cytotoxic chemotherapy[12], only a minority of breast cancers respond to hormonal manipulation and duration of relief may still be short It was in this 'last resort' context that the patients in this series were referred for consideration of palliative radical surgery

Many of the factors known to influence prognosis in primary breast cancer have little bearing on local control or survival after relapse[8] Previous reports have demonstrated that prognosis is unaffected by age, menopausal status, primary tumour stage or initial surgery (incisional or excisional)[9,13]. However, clinical estimation of a tumour's growth rate and biological markers of growth aggressiveness (e.g histological grade and oestrogen receptor status), can provide useful and independent prognostic information[14,15]. Life expectancy after local recurrence generally correlates with the length of the disease-free interval after mastectomy[7–9,11,16]. Both the size and number of sites of local recurrence give an indication of prognosis[8,13].

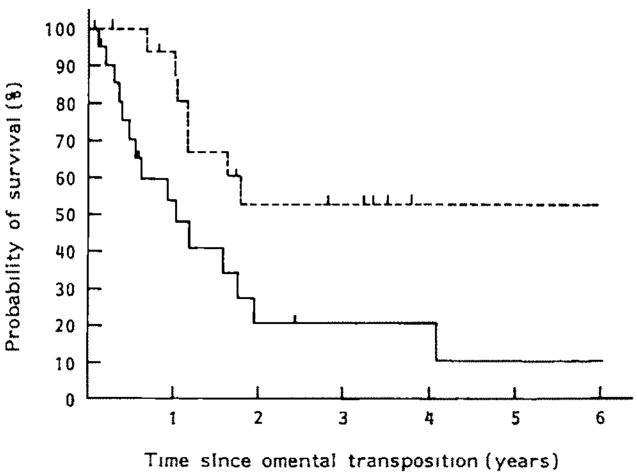
In this series, local control and survival were closely related to tumour diameter. Tumours greater than 10 cm were associated with a particularly poor prognosis. While the area of skin breakdown was partly related to tumour size, ulceration had an additional and independent adverse effect on subsequent local control Satellite cutaneous deposits and lymph node enlargement both predisposed to further chest wall recurrence. Duration of local control was significantly shorter in patients in whom breast cancer had first been diagnosed within the 3 years preceding omental transposition. Somewhat surprisingly, survival was not influenced by the length of this interval.

Radioresistance is a further indication of tumour aggressiveness. Danoff *et al* reported a 62 per cent 3-year survival rate in 40 patients with isolated local recurrences which completely responded to radiotherapy, compared with zero in non-responders[9]. In 52 cases treated by chest wall resection for recurrent breast cancer, Shah and Urban found that earlier radioresistance reduced 5-year survival from 57 to 19 per cent[17]. Our findings are in agreement, in that both local control and survival were very short in three patients whose disease progressed during radiotherapy. The effect of radioresistance on local control was significant and independent of other adverse risk factors.

Life expectancy was significantly reduced in patients previously treated by chemotherapy. This association was independent of the other factors investigated and first became evident some 2 years after omental transposition. The chemotherapy group included both non-responders and those with disease relapse after an initial response to cytotoxic treatment. While this apparent effect may be spurious, Powles *et al*, in a study of combination chemotherapy for advanced breast cancer, reported shorter survival in those who survived beyond 1 year after first relapse[18].

The indications for this type of radical surgery are typically pain and ulceration where life-expectancy can reasonably be expected to exceed 12 months[2]. Palliative surgery should not necessarily be dismissed in patients with distant metastases For 2 years after omental transfer, survival in the small number of patients with known disseminated disease differed little from the remainder, suggesting that we selected patients with relatively slow growing metastases.

The difficulty that may be experienced in controlling or



No. —— 18	15	7	6	2	2	2
at - - -21	9	3	2	2	1	1
risk						

Figure 6 *Survival related to previous cytotoxic chemotherapy (total number of patients, 39),* - - - - - *no chemotherapy (18),* ——— *earlier chemotherapy (21),* P<0 025. *Vertical bars indicate duration of follow-up*

palliating local recurrence emphasizes the importance of optimal treatment to 'high risk' primary breast tumours. In 42 per cent of the patients described, primary cancers were treated with radiotherapy alone Although the probability of local control is widely held to be dose-related, only two of this group received less than 60 Gy. Hence, subsequent failure could not in most cases be attributed to inadequate irradiation. Combining radiotherapy with tumour excision or interstitial implantation of the primary site has been reported to improve control of local disease[19]. While not questioning the rationale of avoiding misplaced surgery in initially 'inoperable' disease, close follow-up is essential to permit early 'salvage' surgery should this become necessary

The list of complications appears extensive but most were of a relatively minor nature. If compression of the omental pedicle in the subcutaneous tunnel is to be avoided, abdominal wall hernias are inevitable in some patients. Separate subcostal incisions are no longer used, as any herniation at the upper end of a mid-line incision overlies the liver and generally presents less of a problem. Where necessary, the omental pedicle can usually be divided after about 3 months and the hernia repaired[20]. However, if extensive radiotherapy has altered the normal development of collateral vascular connections, viability should first be tested by carefully cross-clamping the gastro-epiploic supply[21]. Upper limb lymphoedema was unaffected or occasionally deteriorated, a finding in agreement with other reported results[22].

Greater omentum has immunological and angiogenic properties that confer a healing capability when it adheres to inflamed and damaged surfaces within the peritoneal cavity. Transferred to an infected irradiated site, the scavenging capabilities of omental macrophages together with a dense surface capillary network promote epithelialization and skin graft survival[4]. In general, the objective of omental transposition was the removal of a troublesome malodorous ulcer and not necessarily eradication of malignant disease. In this light, the procedure resulted in symptom relief for an appreciable period and could be judged worthwhile in the majority of patients.

Experience with limited radiotherapy suggests that even apparently small local recurrences are typically an indication of more extensive chest wall disease[11]. Breast cancer commonly permeates through intercostal lymphatic channels into sub-pleural tissues[23] and tumour cells were probably present peripheral to resection in many of the cases presented. While most patients enjoyed a markedly better quality of life, 12 patients developed early recurrence peripheral to the omental graft. This was thought to reflect the biologically aggressive nature of their disease and none survived beyond 2 years after surgery. Very large tumours with diameters greater than 10 cm are probably beyond salvage by this or any other method.

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Management of screen detected ductal carcinoma in situ of the female breast

**R. Carpenter,
P. S. Boulter*,
T. Cooke and
N. M. Gibbs†**

*Department of Surgery, Charing Cross Hospital, London, and Departments of *Surgery and †Histopathology, Royal Surrey County Hospital, Guildford, UK*

Correspondence to.
Mr R Carpenter, University
Department of Surgery,
Southampton General Hospital,
Tremona Road, Southamptom
SO1 6HU, UK

Thirty eight ductal carcinomas in situ *of the female breast detected during the first 7 years of screening by the Guildford Breast Screening Unit have been treated by one surgeon. Twenty-eight cases were treated conservatively and ten by mastectomy. In the group treated conservatively there have been five local recurrences: four as ductal carcinoma* in situ *and one as node negative microinvasive carcinoma. There were no clinical or pathological features that predicted local recurrence, which was detected only by follow-up mammography. Based on these early results, an initially conservative approach to screen detected ductal carcinoma* in situ *is advocated.*

Keywords: Ductal carcinoma *in situ*, breast cancer screening, mammography, local recurrence

Ductal carcinoma *in situ* of the female breast progresses to invasive carcinoma in an unknown proportion of cases and after an unknown time interval; this lack of precise knowledge concerning its natural history has resulted in controversy surrounding the choice of surgical procedure[1]. Conservative surgical operative treatment is favoured by some[2] while others adopt a more radical approach[3]. Retrospective studies based on an initial incorrect diagnosis of benign lesions[4,5] at biopsy have shown that in a proportion of patients with ductal carcinoma *in situ* (up to 40 per cent) there is a transformation to invasive carcinoma. There are no histological features which enable the pathologist to predict invasive transformation of an *in situ* carcinoma[4,5] and this has resulted in an empirical approach to treatment.

Ductal carcinoma *in situ* is detected more frequently after the introduction of screening using mammography[6] and poses a considerable management problem to clinicians involved in treating screened populations. The objective of this paper is to report the results of the treatment of a series of ductal carcinomas *in situ* detected during the first 7 years of the Guildford Breast Screening Programme.

Patients and methods

Women between the ages of 45 and 69 years were enrolled in the Guildford Breast Screening Programme from general practices in Guildford from 1979, and offered screening three times by mammography with clinical examination at 2-yearly intervals and clinical examination alone in intervening years Women with suspected breast lesions are examined and where appropriate fine needle aspiration cytology is performed with ultrasound guidance where necessary All suspicious abnormalities are excised after preliminary localization using the dye contrast method, this is followed by specimen radiology to assess the completeness of resection.

Treatment

Operative procedure is determined by the probable size and position of the lesion and its relationship with the central core of the breast assessed mammographically Small lesions are removed by local or segmental excision and larger lesions by quadrant excision usually with axillary and/or second intercostal space lymph gland sampling and biopsy of the ducts of the central core of the breast[7].

All surgical specimens are examined by one histopathologist using a large section technique and chemical clearance of axillary tissues as an aid to the detection of all axillary lymph glands[6] Further treatment is dependent on the histological report and the results of postoperative mammography at follow-up. Patients with apparent multiquadrant disease and some with diffuse (multifocal) *in situ* ductal carcinoma have been treated by mastectomy Of the 38 patients, four have been treated by radical subcutaneous mastectomy, six by Patey mastectomy and 28 by local excision. Of those managed conservatively, five received quadrant excision and 23 segmental excision. After treatment women are followed up with 6-monthly recall and annual mammographic assessment. The follow-up is complete after a mean of 42 months. The group treated by local excision has a mean follow-up of 38 months and the mastectomy group 55 months, all groups have been followed for between 6 and 84 months

Multicentric, diffuse and focal in situ *carcinoma.* Multicentricity is defined for the purposes of this investigation as multiple malignancies that are not interconnected through the duct system. This criterion can only be determined in mastectomy excisions when different quadrants show malignancy, although the central core ducts are free of disease Multicentricity in limited excisions cannot be proved as all the lesions may be interconnected. *In situ* carcinoma in limited resections was therefore subdivided into diffuse, where the entire duct system was involved, or focal, where isolated ducts showed malignancy although those intervening were normal.

Statistics

Inter-relationships between pathological and clinical characteristics were determined using the Mann–Whitney U test and the χ^2 test employing Yates' correction. Kaplan–Meier life-table analysis was used to calculate the local recurrence rate.

Results

Diagnosis

Thirty eight cases of *in situ* ductal carcinoma without invasive carcinoma were detected by mammography. Malignant cells were found by fine needle aspiration cytology in seven of 20 attempted aspirations

Clinical characteristics

The mean age of the group was 56 years, although the mean age of those who had local excision (54 years) was less than those who had mastectomy (57 years), this was not significantly different

Twenty (53 per cent) patients were premenopausal and 18 (47 per cent) postmenopausal. There were no significant differences between the menopausal status of the treatment groups (*Table 1*).

Site

The majority of ductal carcinoma *in situ* was found in the upper outer quadrants of the breast (*Figure 1*); this is in accordance with the volume distribution of breast tissue by quadrants.

Tumour size

The size of tumours varied between 4 and 55 mm with a mean size of 21 mm. Distribution of tumour size is shown in *Figure 2*. Ductal carcinomas *in situ* treated by mastectomy had a mean diameter of 34 mm which was significantly larger than in

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Table 1 *Clinicopathological characteristics of 38 patients with screen detected ductal carcinoma* in situ

	Menopausal status				Focality		
	Pre	Post	Age (years)	Size (mm)	Focal	Multifocal	Follow-up (months)
Mastectomy	7	3	57	34	3	7	54·6
Excision biopsy	13	15*	54*	16‡	16	12*	37·6*
Non-recurrent	11	12	57	16	13	10	41·8
Recurrent	2	3†	57†	19†	3	2†	18§

*n.s., mastectomy *versus* excision biopsy; †n.s., recurrent *versus* non-recurrent; ‡$P < 0.01$, mastectomy *versus* excision biopsy; §mean time to recurrence

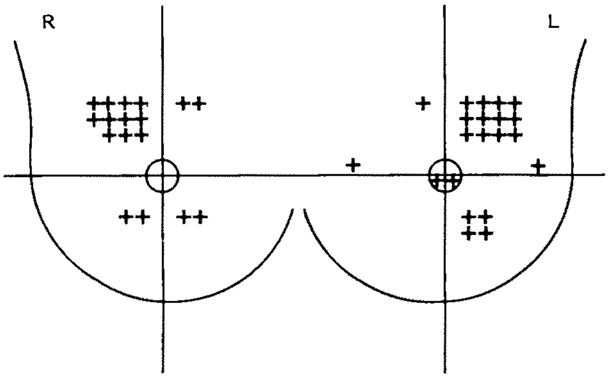

Figure 1 *Distribution of screen detected ductal carcinoma* in situ

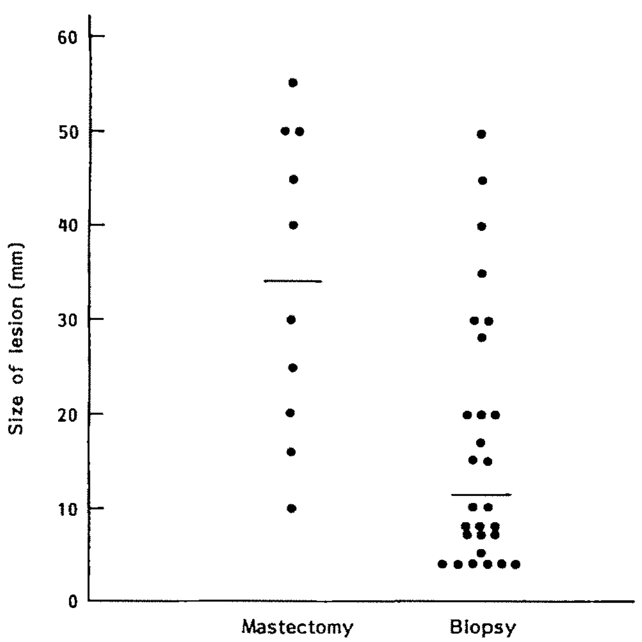

Figure 2 *Size of lesions treated by mastectomy (mean = 34 mm) and biopsy (mean = 16 mm) Mann–Whitney* U *test* z = 2·95, P < 0·01

patients who were treated by excision biopsy, where the mean diameter was 16 mm ($z = 2.95$, $P < 0.01$, Mann–Whitney *U* test).

Multicentric, diffuse and focal lesions

Seven of the ten mastectomies showed either multicentric *in situ* carcinoma or diffuse involvement of one quadrant, and six showed residual ductal carcinoma *in situ* after apparently complete excision biopsy. Diffuse *in situ* carcinoma was found in 12 of the 28 cases of quadrant resection, and focal disease was found in the remainder. Diffuse lesions were significantly larger than focal lesions with a mean diameter of 14 mm ($z = 2.69$, $P < 0.01$, *Figure 3*). All lesions larger than 40 mm were multifocal.

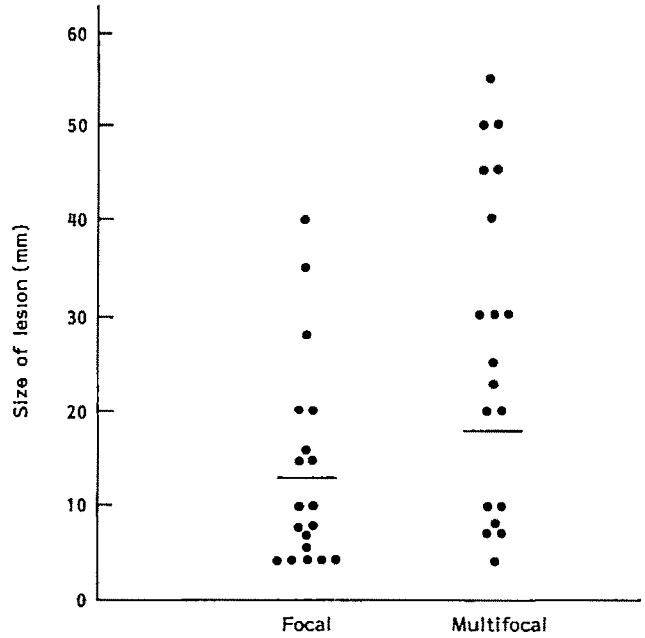

Figure 3 *Size of focal (mean = 14 mm) and multifocal (mean = 28 mm) lesions. Mann–Whitney* U *test·* z = 2.69, P < 0·01

Recurrent disease

All recurrences were detected when mammographic abnormalities (microcalcification) were found at examination which took place at intervals of 6–12 months There were five local recurrences at a mean period of 18 months, with cumulative freedom from recurrence of 77 per cent (life-table analysis, *Figure 4*) at 7 years. Four had been treated with local excision and one by excision followed by radiotherapy. The recurrence in the latter patient showed a microinvasive carcinoma without lymph gland metastases at subsequent Patey mastectomy. The single case of invasive cancer results in an 8 per cent actuarial progression to invasive carcinoma rate over a 7-year period (Kaplan–Meier life-table analysis).

Comparison of recurrent and non-recurrent cases

The mean age of those with recurrence was 57 years, the same as the mean for the non-recurrent group. There was no significant difference between the proportion of premenopausal women in the recurrent (40 per cent) and non-recurrent (48 per cent) groups.

The mean size of the original lesion in those with recurrence (16 mm) was not significantly different from that in patients with no recurrence (19 mm; *Figure 5*). Although all recurrences occurred in the same area of the breast as the original ductal carcinoma *in situ*, the size of the surgical excision specimen (as

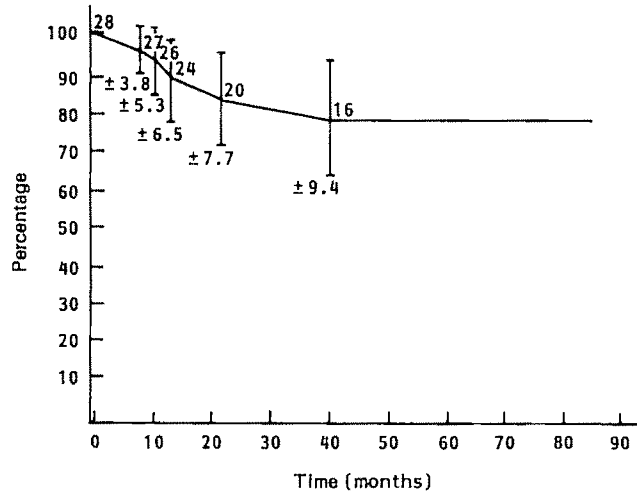

Figure 4 *A life table illustrating the cumulative freedom from recurrence following local resection of screen detected ductal carcinoma* in situ. *The bars show the standard error*

opposed to the lesion itself) in patients who remain disease free (mean 27 cm^2) was not significantly different from the resection specimens in patients who developed recurrent disease (mean 30 cm^2).

Similarly, whether or not the lesion was focal was not related to recurrence; two recurrent cases were originally diffuse and three focal compared with ten multifocal cases remaining in the non-recurrent group of 23 women ($\chi^2 = 0{\cdot}13$, $P > 0{\cdot}5$).

Treatment of recurrent cases

The five instances of recurrent disease were treated by further surgical excision. Two were treated by wide local excision, one by subcutaneous mastectomy, one by quadrant mastectomy with axillary clearance, and one by Patey mastectomy; all remain disease free at a mean time of 22 months (range 6–36 months) since treatment for recurrence.

Discussion

The nearest approximation to the natural history of ductal carcinoma *in situ* comes from retrospective studies where biopsies previously thought to be benign were found to contain ductal carcinoma *in situ*[4,5] Follow-up of these women who received only excision biopsy has shown that up to 40 per cent will progress to invasive cancer in the same breast over 10–15 years. In contrast, small series where symptomatic ductal carcinoma *in situ* has been managed conservatively[8,9] have shown an unacceptable recurrence rate and progression to invasive carcinoma. The introduction of mammography has enabled asymptomatic cases of ductal carcinoma *in situ* to be detected, and in screened populations these lesions comprise 15 per cent of all detected carcinomas[6]; by comparison, symptomatic ductal carcinoma *in situ* is a rare event[2]. There is no precedence for treating screen detected carcinomas as previous studies have been concerned mainly with symptomatic patients[2,8–10] whose disease may show a more aggressive biological behaviour. Lagios *et al*[11] in a selected group of women with mammographically detected lesions <8 mm in diameter has shown a recurrence rate of 15 per cent at a mean follow-up time of 44 months after local excision only. In a further study[12], size has also been used to advise management by lumpectomy and radiotherapy rather than by mastectomy In this study of 51 women, with a mean size of ductal carcinoma *in situ* of 1·4 cm, there was one recurrence but with a short mean follow-up time of 27 months. A conservative approach to screen detected lesions may thus be justified; however, *in situ* carcinoma is a malignancy curable by surgery and so it is perhaps a paradox that cure might be prejudiced by conservative surgery

The management of ductal carcinoma *in situ* detected by screening in Guildford has been primarily conservative with meticulous follow-up examinations by mammography Only one of the cases has progressed to microinvasion and this patient had received adjuvant radiotherapy The role of radiotherapy in management is controversial. Although acceptable local recurrence rates after excision and radiotherapy have been shown in non-controlled series[2,13], ductal carcinoma *in situ* may progress to invasive carcinoma following radiotherapy[2,13,14] and, as shown in our own series, might be resistant to radiotherapy[15,16]. Schnitt *et al.*[17] have reported a high rate of recurrence after radiotherapy for invasive cancer related to residual ductal carcinoma *in situ* adjacent to the excision biopsy site.

Information regarding steroid hormone receptor status of ductal carcinoma *in situ* is scarce[1] and there are no clinical data regarding the place of adjuvant tamoxifen. In this study, four women with segmental excision were commenced on tamoxifen.

The selection of patients for mastectomy was based primarily on the apparent extent of the disease; multiquadrant disease and some multicentric disease were treated by mastectomy. Anderson *et al.*[18] have ascribed a more aggressive behaviour to larger lesions and Lagios *et al.*[19] have shown a relationship between ductal carcinoma *in situ* $>2{\cdot}5$ cm and invasive cancer. Certainly the majority of quadrant sized ductal carcinoma *in situ* contain foci of invasive carcinoma[20] In this study many of the larger quadrant sized lesions have by surgical necessity been removed by mastectomy. However, those which have been suitable for conservative surgery have not shown a tendency to recur (*Figure 4*). Similarly, multifocal disease in the biopsy specimen is not related to recurrence It is of crucial importance to ensure that the central core of the breast is not involved by ductal carcinoma *in situ* before limited resection is performed and to this end all quadrant resections were accompanied by a central core and nipple core biopsy in this series.

There has been one only case of recurrent invasive cancer in the series, giving a 7-year actuarial progression rate of 8 per cent. Although the follow-up period is short, this tends to support the view that asymptomatic ductal carcinoma *in situ* is a less aggressive tumour than symptomatic ductal carcinoma *in situ*. Nevertheless, follow-up mammography examinations detected the local recurrence at an early stage of invasion before lymph gland metastases had occurred

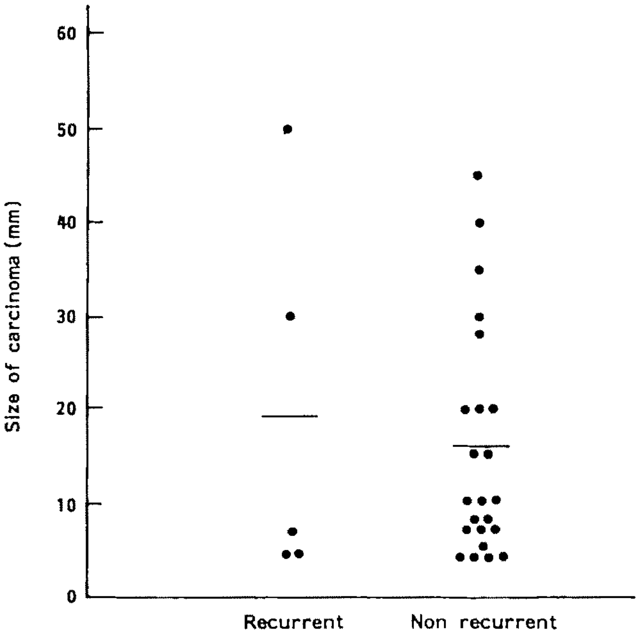

Figure 5 *Size of recurrent (mean = 19 mm) and non-recurrent (mean = 16 mm) ductal carcinomas Mann–Whitney* U *test. difference not significant*

Residual ductal carcinoma *in situ* was found in about two-thirds of breasts which were eventually removed by mastectomy, and this is comparable to previous studies[21,22]. There is therefore the implication that not all residual disease is biologically active[2], but breast cancer can have a protracted course, requiring long-term follow-up in all cases.

Using mammographic and pathological criteria to determine conservative treatment for apparently focal lesions, only one case of recurrent invasive cancer has occurred in 28 women with ductal carcinoma *in situ* treated conservatively and followed over 7 years. Follow-up is relatively short (mean 38 months); however, estimates of probability of local recurrence suggest that this will not alter appreciably with longer follow-up[2]. Annual mammography has detected all recurrences at an early stage (four as ductal carcinoma *in situ* and one as microinvasive cancer) and it is unlikely that more frequent mammography will improve detection rates of recurrence.

Our early findings indicate that screen detected ductal carcinoma *in situ* may behave in a more indolent manner than symptomatic ductal carcinoma *in situ*. Current preference for radical management may require re-evaluation, particularly in the light of a more conservative approach to the management of invasive breast cancer. Where good mammographic follow-up facilities exist, initial treatment of the majority of screen detected ductal carcinoma *in situ* has been safely accomplished by simple excision To date, any recurrence has been detected and dealt with at an early stage.

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Arm morbidity within a trial of mastectomy and either nodal sample with selective radiotherapy or axillary clearance

R. J. Aitken,
M. N. Gaze*,
A. Rodger*,
U. Chetty and
A. P. M. Forrest

University Department of Surgery, The Royal Infirmary, Edinburgh and
**Department of Clinical Oncology, Western General Hospital, Edinburgh, UK*
Correspondence to:
Sir Patrick Forrest, Department of Surgery, The Royal Infirmary, Edinburgh EH9 3YW, UK

The aim of this study was to assess upper limb morbidity following treatment for operable breast cancer. Patients were randomized to either mastectomy and axillary clearance (40 women: 12 with axillary nodal metastasis and 28 without axillary metastasis) or mastectomy and axillary sampling (54 women). Adjuvant radiotherapy was delivered to those in whom the sample revealed axillary nodal metastasis (28 women) but not to those with no axillary nodal metastasis (26 women). A subjective assessment of the state of the arm was made using a standard questionnaire. Objective assessment included upper and forearm circumference, shoulder joint mobility and assessment of power in the pectoralis muscle. The mean age was 56·8 years (range 33–77 years) and the mean elapsed time from treatment was 5·72 years (range 4·0–7·5 years). Subjective limb oedema was greatest in those who had axillary lymph node metastasis but there was no objective difference. Subjective joint mobility was reduced in the women who received radiotherapy and this was confirmed by objective assessment ($P < 0.05$). The objective reduction in arm mobility was related to the treatment rather than the axillary lymph node status. There was no difference in power. In this study women receiving adjuvant radiotherapy had significantly reduced shoulder mobility. This may have implications for current conservation studies using adjuvant radiotherapy.

Keywords: Breast neoplasia, surgery, morbidity

The treatment of breast cancer with breast conservation has led to a resurgence in the use of radical radiotherapy both to the residual breast and as an alternative to surgical clearance of the axilla[1,2]. Surgery remains the principal initial treatment for early breast carcinoma but its extent and the role of radiotherapy, particularly in the management of the axilla, is still controversial. In the UK many surgeons still prefer to perform a mastectomy with either surgical clearance of the axilla or node sampling with radiotherapy only if there are metastatic deposits in the axillary nodes[3–5].

Late upper limb oedema is a recognized complication of either radiotherapy or surgery[6] and is most severe if the irradiated axilla has also been surgically cleared[7,8]. Previous studies assessing arm morbidity are difficult to interpret. For example, the influence of the initial selection is unclear and women with known local or distant recurrent disease, itself a cause of limb morbidity, were not always excluded[7,9,10]. Radiotherapy now utilizes megavoltage rather than orthovoltage X-rays which may require differing techniques with significantly different biological effect. Treatment with either radiotherapy or surgical clearance of the axilla does not appear to confer any survival advantage[11], so their relative morbidity assumes greater importance.

It therefore seemed appropriate to reappraise the morbidity of axillary treatment in the randomized group of women included in the Edinburgh sample-or-clearance trial[12,13]. In this trial women with operable breast carcinoma (T_{0-2}, $N_{0 \text{ or } 1}$, M_0) were prospectively randomized to be treated either by mastectomy and axillary clearance or mastectomy and node sampling, with adjuvant radiotherapy to the axilla being given only to women with metastatic deposits. Thus, four groups of women were available for assessment of morbidity: (1) women with axillary nodal metastasis treated by surgical axillary clearance (C+), (2) women without axillary nodal metastasis treated by surgical axillary clearance (C−), (3) women with axillary nodal metastasis treated by axillary node sample and radiotherapy (R), (4) women without axillary nodal metastasis treated by axillary sampling only (S).

Patients and methods

Only women in the Edinburgh sample-or-clearance trial known to be free of local or systemic disease were considered for this study. An unselected group of women, chosen alphabetically, were sent an invitation to attend a special clinic. Non-respondents received a further letter or telephone call Details of the initial randomization, surgery and radiotherapy were confirmed from trial and radiotherapy records only at the conclusion of the study. The women were specifically requested not to volunteer the nature of their treatment although in some it was obvious on clinical examination that they had received radiotherapy

At the clinic a single observer (RJ A.) recorded personal details and completed a standard questionnaire which recorded subjective impairment of daily activity. Objective assessment of arm swelling and shoulder mobility was assessed by measuring arm circumference 15 cm above and 10 cm below the olecranon[7,9] while the woman sat with her hands on her hips The median of three measurements was recorded Shoulder joint mobility was assessed by four methods: (1) adduction with internal rotation and (2) abduction with external rotation were assessed by measuring the woman's ability to reach behind her back and up or down the spine respectively using the C7 spinous process as the reference point; (3) the difference (between the treated and the non-treated arm) in height reached whilst standing face against a wall and stretching as high as possible; (4) measurement of an abduction movement without shoulder rotation whilst lying on a flat, hard surface. The power (centimetres per kilogram) of pectoralis major was assessed by the repeated lifting of a 3·5 kg weight as fast as possible over 45 s The treated and non-treated arm was assessed in each patient.

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Table 1 *Personal details of patients assessed*

	R	S	C+	C−
No of patients	28	26	12	28
Age (years)*	57·2 (9·4)	58·0 (10·8)	57·7 (7·3)	49·3 (10·6)
Elapsed time (years)*	5·5 (1·0)	5·9 (1·0)	5·9 (1·1)	5·3 (1·1)
Surgery to dominant/non-dominant limb	11/17	11/15	10/2	15/13
Prosthetic implant	14	10	5	10
Surgical complications				
Wound infection	0	1	3	3
Lymphocele or haematoma	4	8	4	4

* Values are mean (s.d.). R, axillary nodal metastasis treated by axillary node sample and radiotherapy; S, axillary sampling only without nodal metastasis, C+, axillary clearance with nodal metastasis; C−, surgical axillary clearance without nodal metastasis

Table 2 *Subjective response to the questionnaire*

	R	S	C+	C−
No. of patients	28	26	12	28
Arm swelling				
Nil	17	23	8	22
Intermittent	2	1	1	1
Persistent	9 (32)	2 (8)	3 (25)	5 (18)
Mobility				
Normal	12	24	12	22
Reduced	16 (57)	2 (8)	0	6 (21)
Interference with daily activities				
Nil	16	24	12	24
Occasional	8	2	0	4
Severe	4 (14)	0	0	0

Values in parentheses are percentages. R, axillary nodal metastasis treated by axillary node sampling and radiotherapy, S, axillary sampling only without nodal metastasis, C+, axillary clearance with nodal metastasis; C−, surgical axillary clearance without nodal metastasis

The treated and non-treated arms were compared within each group and in a second analysis the differences between the treated and non-treated arms were calculated and compared between the four groups.

Radiotherapy

In the original ('old') radiotherapy technique the supraclavicular fossa, shoulder and axilla were treated with semiopposed fields to a dose of 42·5 Gy in ten alternate-day fractions using megavoltage radiation with bolus to achieve dose homogeneity. Despite dose reduction to 40 Gy and the introduction of humeral shielding, late morbidity in the form of telangiectasia, subcutaneous fibrosis and osteonecrosis was still apparent

In 1982 the radiotherapy technique was revised to give a maximum dose of 45 Gy in 20 fractions over 4 weeks with megavoltage radiotherapy (the 'new' technique) The posterior field was reduced in size just to cover the axilla. Bolus was no longer used

Data handling and analysis

The data were stored and analysed on an Excel® (Microsoft Corporation, California, USA) spreadsheet using an Apple MacIntosh SE® (Apple Computer Incorporated, Cupertino, California, USA) microcomputer Statistical analysis was by Student's *t* test, the χ^2 test and the test for trend.

Results

The personal data of the women in this study are shown in *Table 1*; the study group represent 33·2 per cent of the women in the Edinburgh sample-or-clearance trial who were alive and disease free. Women who had an axillary clearance and were node negative differed from the other groups in that ten of the 12 carcinomas were in the right breast and the dominant arm was therefore more frequently implicated.

Subjective assessment (Table 2)

Although subjective arm swelling was similar in the women who were node positive (R and C+) and greater than in the women who were node negative (S and C−) this difference was not significant (test for trend: R *versus* C+, $P = 0·9$; S *versus* C−, $P = 0·55$; C+ *versus* C−, $P = 0·4$). The oedema was generally of a minor nature and no woman was inconvenienced by limb swelling. Significantly more women (16 of 28, 57 per cent) who received radiotherapy noted some shoulder stiffness (χ^2 test: R *versus* C+, $\chi^2 = 9·17$, $P = 0·003$; S *versus* C−, $\chi^2 = 1·07$, $P = 0·30$; C+ *versus* C−, $\chi^2 = 1·58$, $P = 0·21$). In four women (14 per cent) this significantly influenced their daily activities (test for trend: R *versus* C+, $P = 0·03$; S *versus* C−, $P = 0·74$; C+ *versus* C−, $P = 0·40$). Women in all groups commented that the treated limb easily tired but none found this a significant impediment.

Table 3 *Shoulder joint mobility (range of movement)*

	P values		
Group assessed	Abduction/ external rotation	Adduction/ internal rotation	Abduction only
Comparison within each group (treated *versus* non-treated arm)*			
R	<0·001	0·001	<0·001
S	0·509	0·507	0·074
C+	0·408	0·024	0·174
C−	0·473	0·383	0·065
Difference between the groups (treated minus non-treated)†			
R *versus* C+	0·033	0·623	<0·001
S *versus* C−	0·340	0·297	0·956
C+ *versus* C−	0·700	0·029	0·519

Statistical analysis was by Student's *t* test. * The treated arm was always less mobile than the non-treated arm; † the range of movement in the first group was always less than the second group R, axillary nodal metastasis treated by axillary node sampling and radiotherapy; S, axillary sampling only without nodal metastasis; C+, axillary clearance with modal metastasis; C−, surgical axillary clearance without nodal metastasis

Objective assessment

There was no difference in any of the parameters assessed between the non-treated (control) arms of the four groups. Within each group the treated and non-treated arms were compared. There was no significant difference in limb circumference. In the node positive women, all shoulder joint movements were reduced in the women who received radiotherapy but in women who had an axillary clearance, only adduction and internal rotation was reduced (*Table 3*). In the node negative women there was no difference in shoulder mobility between the treated and non-treated arms (*Table 3*).

The difference between the treated and non-treated arms was calculated and women with similar axillary nodal status (R *versus* C+ or S *versus* C−) were compared. Women who had a surgical axillary clearance, regardless of nodal status, were also compared (C+ *versus* C−). There was no significant

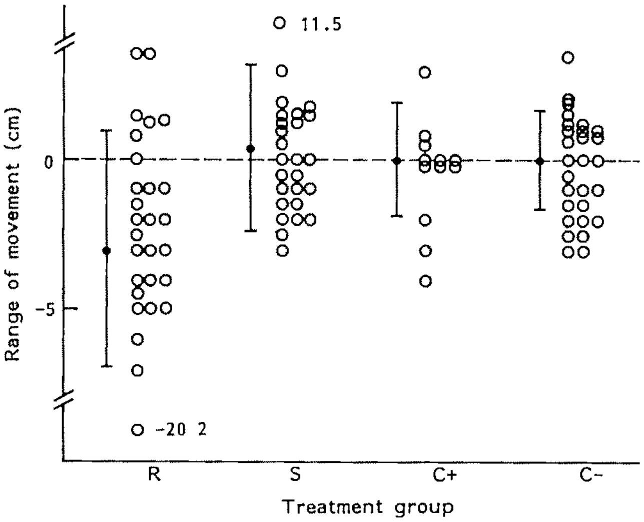

Figure 1 *The difference (mean and s d) in the range of movement (non-treated minus treated arm) with abduction and external rotation R, axillary nodal metastasis treated by axillary node sample and radiotherapy, S, axillary sampling only without nodal metastasis, C+, axillary clearance with nodal metastasis, C−, surgical axillary clearance without nodal metastasis. The range of movement in women receiving radiotherapy is significantly reduced Student's* t *test R* versus *C+*, t = −2·21, P = 0·033, *S* versus *C−*, t = −3·55, P = 0·340, *C+* versus *C−*, t = 0·39, P = 0·700

difference in limb circumference. In the node negative women there was no significant difference in the range of shoulder movement but, in the node positive women, mobility in women who received radiotherapy was significantly reduced in two of three movements when compared with women who had an axillary clearance (*Table 3*). As an example, the range of movement for abduction with external rotation is shown as a scatter graph in *Figure 1*.

There was no significant difference between any groups when measuring the height reached up the wall. The power of pectoralis major (treated *versus* non-treated arm) was reduced in women who received radiotherapy (Student's *t* test: $t = -2{\cdot}67$; $P = 0{\cdot}013$) but there was no difference between the four groups.

This analysis revealed no major difference between the women who had a clearance; the two groups were then combined (C+ and C−, 40 women) and compared with the women who had a node sample. This second analysis, with the women who had a clearance in a single group, confirmed there was no difference in arm circumference between the groups. The range of shoulder movement in women who had an axillary clearance was significantly greater than the women who had radiotherapy but there was no significant difference in the range of shoulder movement when compared with the women who had a node sample only.

Women who received radiotherapy were subdivided according to the radiotherapy technique used (16 and 12 women in the old and new techniques respectively). The trend suggested that those treated by the old technique had greater impairment of shoulder mobility but the numbers were small and these women had the longest follow-up time.

There was no consistent effect resulting from surgery to the dominant or non-dominant arm. There was no evidence to suggest that these differences were related to the presence of an implant.

Discussion

We have demonstrated that shoulder joint mobility in women who received radiotherapy to the chest wall and axilla was significantly impaired when compared with those in whom the axilla was only sampled or surgically cleared. This finding may have important implications for women now being offered breast conservation when the axilla is managed with radiotherapy rather than surgery[1,2]. The median follow-up time (5–6 years) in this study is short and, as the late complications of radiotherapy are irreversible and may be progressive, our results probably represent a conservative assessment of potential morbidity.

This study was deliberately designed to relate to the women's daily activities. Assessment of shoulder joint movement in a single direction is of limited value as almost all upper limb movements involve the whole shoulder girdle. In this study, four of 28 women (14 per cent) receiving radiotherapy had to make a major readjustment in life-style, such as giving up a recreational activity or using their other arm.

The principal difference between the women in this study was the nodal status: all the women receiving radiotherapy were axillary node positive and those who had a node sample only were all axillary node negative, whereas women who had axillary clearance could be either node positive or negative. These results reflect differences of treatment rather than the node status. Although there was no difference between women irradiated by the old and new techniques, evidence from a larger group of women suggests that rib necrosis and pulmonary fibrosis have been reduced with the introduction of the new technique.

Unlike previous reports[5,6,10], we did not find that arm oedema was prominent in this study and although subjectively greater in those with axillary lymph node metastasis this difference was not significant. Even on direct questioning, no woman volunteered swelling of any practical importance. There is no obvious explanation for the lack of arm swelling in this study but longer follow-up is required. Although others[5,6] have assessed limb oedema by volumetric methods, we have found that the wide normal variation in arm volume makes reliable comparisons difficult unless there is a preoperative assessment as a baseline; this was not available with these women.

Although there is no unanimity on the best way to treat the axilla, the morbidity secondary to radiotherapy is of concern and must be balanced against a possible increased incidence of axillary recurrence, although in this study there was no difference in the four groups[13]. As it is more difficult to perform a complete axillary nodal clearance when the breast is conserved, it will be important to assess women treated in this manner and Edinburgh women being entered into the current Scottish Conservation Trial are presently having a wide local excision and being randomized to either surgical axillary clearance or nodal sample with selective radiotherapy.

In conclusion, this study has demonstrated that shoulder joint mobility is significantly reduced following treatment of the axilla by nodal sample and radiotherapy rather than surgical axillary clearance. When we perform a mastectomy we now prefer to undertake an axillary node clearance.

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Technique for operative cholangiography after endoscopic sphincterotomy

M. N. Vipond, C. Gatzen, J. N. Thompson and H. A. F. Dudley

Academic Surgical Unit, St. Mary's Hospital,
London W2 1NY, UK
Correspondence to: Mr M N. Vipond

With the use of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy for common bile duct stones, cholangitis, papillary stenosis and in gallstone pancreatitis, an increasing number of patients will come to cholecystectomy with an incompetent sphincter of Oddi The majority of such operations are performed some time after sphincterotomy when the acute illness has resolved. For these patients the importance of accurate cholangiography is evident We present a simple, safe and effective method of operative cholangiography.

Technique

The cystic duct is dissected in the usual manner. The duct is opened and a 5 Fr biliary Fogarty catheter (Edwards Laboratories, Irvine, California, USA) is passed along the duct system to enter the duodenum via the sphincterotomy The balloon is inflated and the catheter drawn back on to the ampulla to occlude the sphincterotomy. Cholangiography is performed by direct puncture of the common bile duct using a 23 gauge 'butterfly' needle (Abbott Ireland Ltd , Sligo, Ireland) Films are obtained in the standard way and a final film is taken with the balloon deflated to confirm free flow of contrast into the duodenum. A cholangiogram obtained in this way is shown in *Figure 1*.

Discussion

ERCP and sphincterotomy have become established management for patients presenting with common bile duct stones. In patients with concomitant medical conditions endoscopic sphincterotomy may be definitive treatment, but a proportion of patients will come to cholecystectomy because of failure to clear the duct, or with persisting or recurrent symptoms[1]. In patients with severe acute pancreatitis of gallstone aetiology it has recently been proposed that urgent (within 72 h) ERCP should be carried out and, if stones are present, endoscopic sphincterotomy performed[2]. After resolution of the acute episode of pancreatitis cholecystectomy is recommended during the same hospital admission[3,4].

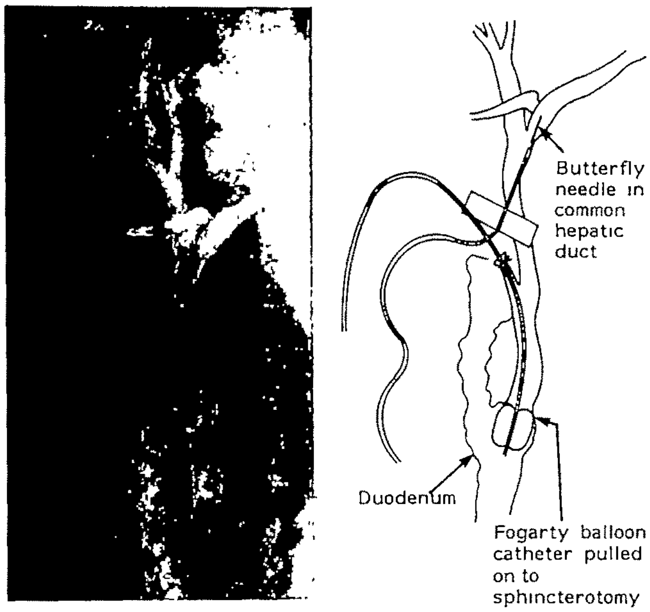
Butterfly needle in common hepatic duct
Duodenum
Fogarty balloon catheter pulled on to sphincterotomy

Figure 1 *An operative cholangiogram obtained by the method described and a schematic representation of the cholangiogram*

In patients who have had an endoscopic sphincterotomy for duct stones it is important that good-quality operative cholangiograms are obtained. However, the presence of a sphincterotomy makes it difficult to obtain filling of the whole biliary system. The use of the technique described here overcomes this problem.

Acknowledgements

We wish to thank Mrs Sheila Jones for preparation of the illustration.

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Graft occlusion following aortofemoral bypass for peripheral ischaemia

A. R. Naylor*, A. K. Ah-See and J. Engeset

The Vascular Surgical Unit, Aberdeen Royal Infirmary, Forresterhill, Aberdeen, UK

Correspondence to:
Mr J. Engeset

Over a 10-year period, 241 patients with non-aneurysmal aortoiliac disease underwent aortofemoral bypass to 476 limbs. Four patients (1·7 per cent) occluded their grafts within 30 days of surgery, while 25 (10·4 per cent) suffered late graft occlusion. Postoperative occlusions were associated with significant morbidity and only one patient avoided major limb amputation or death. Overall, 46 episodes of graft thrombosis involving 51 graft limbs were encountered, the most common underlying cause being pre-existing or progressive multilevel distal occlusive disease. The overall cumulative graft patency rates were 95 and 87 per cent at 1 and 5 years respectively. Cumulative 5-year patency was significantly higher in patients presenting with claudication (91 per cent) than in patients presenting with rest pain (77 per cent) or ulceration and/or gangrene (71 per cent). Patients with evidence of multilevel distal occlusive disease at the time of aortic surgery had a significantly higher incidence of occlusion compared with those in whom there was no significant distal disease. In 35 episodes of occlusion (76 per cent), surgery was undertaken to restore limb blood flow, being successful in all but one case, with the most commonly performed procedure being graft limb thrombectomy. Seven of 28 patients (25 per cent) ultimately required major limb amputation and three patients died as a direct consequence of graft thrombosis.

Keywords: Aortofemoral bypass, graft occlusion

In the original 1952 report by Voorhees *et al.*[1] on the use of Vinyon 'N' cloth as a prosthetic replacement of the aorta, it was reported that 20 per cent of the experimental animals developed graft occlusion. In the intervening years, aortofemoral bypass has adopted an accepted place in the management of aortoiliac occlusive disease, but thrombosis remains the most commonly encountered graft-related complication during follow-up. This paper details our experience of graft occlusion in a consecutive series of 241 patients who underwent aortofemoral bypass over a 10-year period.

Patients and methods

A retrospective review was undertaken of 245 patients with non-aneurysmal aortoiliac occlusive disease who underwent aortofemoral bypass between January 1975 and December 1984 Four patients were excluded from analysis as no follow-up data were available. Patients have been regularly reviewed at the Vascular Clinic after surgery, although in a small number of patients, where long distances precluded clinic attendance, a questionnaire was completed by the family practitioner. The mean period of follow-up was 51 months (range 4–120 months) There were 171 men (71 per cent) with a mean age of 59·8 years (range 40–78 years) and 70 women (29 per cent) with a mean age of 59·9 years (range 45–76 years). Disabling claudication was the indication for surgery in 71 per cent of patients, while 29 per cent presented for limb salvage. The proximal aortic anastomosis was fashioned end-to-end in 160 patients (66 per cent) and end-to-side in 81 (34 per cent). An infrainguinal distal anastomosis was performed in 99 per cent of limbs; ten patients (4 per cent) underwent synchronous femorodistal bypass.

At the time of aortofemoral bypass, 207 limbs had no evidence of significant outflow or distal vessel disease, while 85 limbs were noted to have an isolated superficial femoral artery (SFA) occlusion in association with three-vessel run-off below the knee. Combined SFA occlusion, profunda femoris stenosis and/or occlusion and only one- or two-vessel run-off below the knee were present in 38 limbs

Statistical analysis was by Fisher's exact test and the log rank test with χ^2 analysis.

Results

Twenty-eight patients (11·6 per cent) had a total of 46 episodes of graft occlusion involving 51 graft limbs during follow-up. Twenty-four were men (mean age 56·9 years, range 42–74 years) and four were women (mean age 55 years, range 49–67 years). Seventeen patients had undergone a proximal end-to-end anastomosis and 11 an end-to-side. Four patients (1·7 per cent) suffered a graft occlusion within 30 days of surgery (one patient twice), while a further 25, including one patient whose graft occluded postoperatively, developed late graft occlusion. Two of the limbs with postoperative graft occlusion were noted to have poor distal run-off vessels, while no obvious underlying cause was identified in one patient. The remaining graft occluded in association with graft sepsis. Of the four patients, one died after a successful thrombectomy and femorodistal bypass and two required major limb amputation.

An acutely ischaemic leg was the presenting feature in 70 per cent of the 41 episodes of late occlusion, 30 per cent presenting with worsening claudication (13 per cent acute, 17 per cent a worsening of pre-existing claudication). The left graft limb was occluded in 65 per cent of episodes, the right in 24 per cent ($P = 0·007$), bilateral occlusions being present in five episodes. The times to graft occlusion with respect to the 46 episodes are detailed in *Table 1*, 30 per cent having occurred within 1 year of surgery and 87 per cent within 3 years.

Inflow pathology accounted for three (6 per cent) of the occlusions· two as a consequence of proximal aortic stenoses and one as a result of kinking of the graft. Systemic or other causes may have predisposed the graft to occlude in 12 episodes In six, a hypercoagulable state was proposed as the underlying cause (platelet dysfunction in two, polycythaemia in two, tumour induced thrombogenicity in two) Three patients

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* *Vascular Research Unit, Edinburgh Royal Infirmary, UK*

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Table 1 *Timing of 46 episodes of graft occlusion*

Time from aortofemoral bypass (months)	No. of episodes
<1	5
1–12	9
13–24	17
25–36	9
37–48	4
49–60	1
61–72	0
73–84	1
>84	0

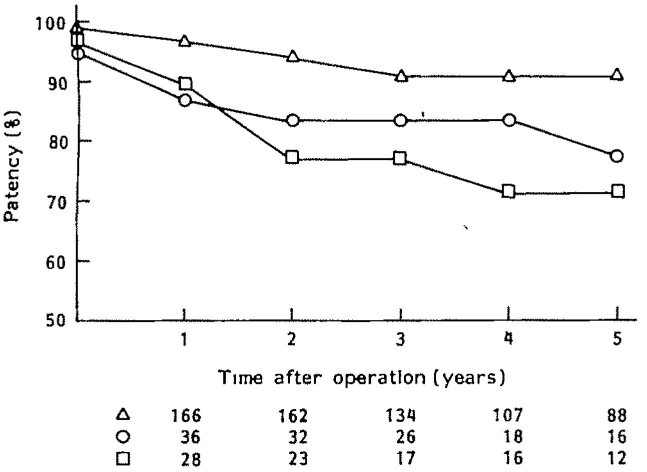

Figure 1 *Cumulative graft patency relative to mode of presentation.* △, *Claudication,* ○, *rest pain;* □, *ulceration and/or gangrene The numbers of patients at risk are given*

suffered graft occlusion in association with graft sepsis, while the cause was unknown in one patient. Two patients presented with a myocardial infarction and subsequently their grafts occluded as a consequence of prolonged hypotension, the grafts being noted to be patent on admission. The largest single group included those with outflow and distal vessel disease (31 episodes, 67 per cent). In two episodes, a stenosis at the femoral anastomosis was responsible for the occlusion, while in 29, there was evidence of pre-existing (58 per cent) or progressive (42 per cent) distal occlusive vessel disease. Three patients occluded their grafts while on therapeutic doses of anticoagulants, having been started on warfarin after a previous episode of graft thrombosis. There was no significant difference in 5-year graft patency rates: in men (84 per cent) and women (91 per cent, $P < 0{\cdot}2$), smokers (80 per cent) and non-smokers (91 per cent, $P < 0{\cdot}1$), and those with a proximal end-to-end anastomosis (87 per cent) as opposed to an end-to-side anastomosis (84 per cent, $P < 0{\cdot}5$). Patients presenting with claudication (*Figure 1*) had a significantly better cumulative 5-year patency rate (91 per cent) than those initially referred with rest pain (77 per cent, $P < 0{\cdot}05$) or ulceration and/or gangrene (71 per cent, $P < 0{\cdot}001$). There was no statistically significant difference in cumulative patency between the latter two groups of patients.

Claudicants who smoked postoperatively had a significantly lower 5-year patency rate (87 per cent) than non-smokers (96 per cent, $P < 0{\cdot}05$). Patients who smoked after limb salvage surgery had a lower 5-year patency (65 per cent) than non-smokers (82 per cent), although the difference did not reach statistical significance.

Outflow and distal vessels that showed no evidence of occlusive disease at the time of aortic surgery (*Figure 2*) had significantly better 5-year patency rates (97·7 per cent) than limbs with an isolated SFA occlusion (91·2 per cent, $P < 0{\cdot}05$). The worst patency rates occurred in patients with a SFA occlusion in association with profunda femoris occlusion or stenosis and only one- or two-vessel run-off below the knee (5-year patency 67 per cent).

In 11 of the 46 episodes of occlusion, no surgical intervention was undertaken. In four patients this was because they had presented late and were living within their claudication distances. Three grafts reoccluded in the postoperative period after thrombectomy and were not subjected to further clearance because of poor distal vessels, while a further two patients were not operated on as their diseased vessels would not support the graft. The two patients whose grafts occluded after myocardial infarction were not submitted to surgery; one of the patients subsequently died.

In 35 episodes of occlusion (*Table 2*) surgical intervention was undertaken. In four, graft thrombectomy proved impossible and limb blood flow was restored by extra-anatomical bypass. Three patients (two with coexistent sepsis) underwent either total or partial graft excision as the primary procedure, limb blood flow being restored in two and poor distal vessels precluding reconstruction in the third.

In 28 episodes (80 per cent), graft thrombectomy was successfully undertaken and in 14 cases, no additional procedure was performed. Despite undergoing a successful thrombectomy, the grafts of a significant proportion of patients subsequently reoccluded with one patient suffering six episodes of thrombosis. Cumulative patency after the first successful graft thrombectomy was 68 per cent at 1 month, 48 per cent at 1 year and 30 per cent at 5 years If, however, the data are expressed as cumulative 'extended' patency in the manner of Brewster *et al.*[2] (this allows for repeatedly successful graft thrombectomies to be included with the patent graft limb group after the first

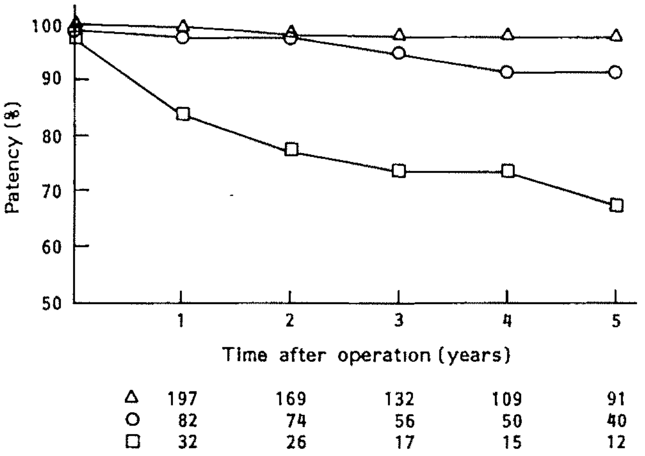

Figure 2 *Cumulative limb patency relative to preoperative angiogram* △. *No distal disease;* ○, *isolated superficial femoral artery occlusion,* □, *multilevel occlusive disease. The numbers of limbs at risk are given*

Table 2 *Surgical management in 35 episodes of occlusion*

Graft thrombectomy successful	28
Thrombectomy alone	14
Femorodistal bypass	6
Revision distal anastomosis	4
Proximal inflow revision	2
Revision of kinked graft	1
Femorofemoral + femorodistal bypass	1
Graft thrombectomy unsuccessful	4
Femorofemoral bypass	3
Axillofemoral bypass	1
Graft limb or total graft excision	3
Prosthetic graft limb interposition	1
Biaxillobipopliteal bypass	1
No graft limb reconstruction	1

thrombectomy), 90 per cent of grafts were patent at 1 month, 84 per cent at 6 months and 71 per cent at 5 years

Seven of 28 patients (25 per cent) ultimately required major limb amputation (five above-knee, two below-knee) including the two patients whose amputations followed postoperative occlusions Six had evidence of poor distal run-off, in three the main graft occluded in the postoperative period after an earlier graft thrombectomy and in two it was in association with graft sepsis Only one patient required amputation in the presence of a patent aortic graft having undergone a successful thrombectomy and femorodistal bypass, although this patient subsequently died from acute renal failure. Three patients died as a direct consequence of graft occlusion and its sequelae. Acute renal failure was the cause of death in two patients, one in the postoperative period after successful thrombectomy and femorodistal bypass, while the second with graft sepsis died after graft excision and revascularization. The remaining patient suffered a myocardial infarction after an unsuccessful graft clearance and axillofemoral bypass. There have been no deaths after thrombectomy alone

Discussion

Thrombosis was the most commonly encountered graft-related complication in patients undergoing aortofemoral bypass in our unit[3]. Our incidence of 1·7 per cent in the postoperative period compares favourably with the results of other studies[4–9], although it is significant that only one of the four patients avoided either death or major limb amputation. Acute limb ischaemia was the presenting feature in 70 per cent of late episodes and this is in accordance with the experience of others[2,7,8], emphasizing the importance of early referral and management We found no significant differences in cumulative patency rates: between men and women, in the different modes of proximal anastomosis, in the presence or absence of diabetes, in the presence or absence of hypertension; although others have reported a higher incidence of graft occlusion in men[2], women[6] and end-to-side proximal anastomoses[11]. As with Najafi *et al.*[7], we found a higher incidence of thromboses involving the left graft limb. While others have reported a significant association between smoking and graft occlusion[4,6,10], the difference did not reach statistical significance in this study Claudicants who smoked postoperatively were significantly more likely to occlude their grafts than non-smokers, and while similar trends were evident in the limb salvage group the relatively small numbers involved did not reach statistical significance. Patients presenting with claudication had a significantly lower incidence of graft occlusion than patients undergoing surgery for limb salvage, reflecting the fact that claudicants have better distal vessels at the time of aortic surgery than limb salvage patients Satiani *et al.*[10] found a higher incidence of thrombosis in patients with rest pain as opposed to those with ulceration or gangrene, although no significant difference was evident in this study

It is now generally accepted that the fate of the graft is closely related to the state of the vessels distal to the femoral anastomosis[2,8,9] and our experience is in accordance with this. While Nevelsteen *et al.*[8] found no significant difference in subsequent graft occlusion in patients with evidence of SFA occlusion at the time of aortofemoral bypass, this was not borne out in this study Patients with an isolated SFA occlusion had a significantly worse cumulative limb patency rate than patients having limbs with no evidence of distal occlusive disease. These findings are similar, but not as marked as those reported by Harris *et al.*[12], where the cumulative 5-year patency was 98 per cent in patients with no significant distal vessel disease, falling to 65 per cent where the SFA was occluded

Malone *et al.*[9] noted that all patients with combined profunda and trifurcation disease thrombosed their grafts within 5 years and that, in the absence of distal disease, only 5 per cent of grafts would occlude during follow-up. Those patients in this study with combined SFA and profunda femoral artery disease in association with diseased run-off vessels below the knee fared worst of all with a cumulative 5-year patency rate of 67 per cent.

Current concepts in the management of graft occlusion include thrombectomy (with or without synchronous distal reconstruction), graft limb excision and prosthetic interposition, extra-anatomical bypass and thrombolytic therapy[2] We have had no experience of the latter. The recent study of 157 episodes of graft limb occlusion by Brewster *et al.*[2] has led them to advocate thrombectomy as a consequence of 'increased confidence in its feasibility and reliability'. In their series, thrombectomy was successful in all postoperative occlusions and in 95 per cent of late thromboses. Although the cumulative patency of the cleared grafts was only 47 per cent at 5 years, they found that with repeated thrombectomies, the cumulative 'extended' patency was 74 per cent at 5 years These findings are similar to our own experience

Our current policy is to undertake graft limb thrombectomy whenever possible Patients who present late and who are able to live within their claudication distance, having developed a satisfactory collateral circulation, are not generally referred for surgery. Those patients whose grafts reocclude in the postoperative period after thrombectomy are not subjected to further surgery if the distal vessels are poor. Those patients whose grafts remain occluded after attempted thrombectomy are considered for extra-anatomical bypass Repeat thrombectomies are performed as they are required, at which time distal reconstruction may be considered particularly for those with critical ischaemia. In our experience however, these patients usually have such poor distal vessels that reconstruction is often not possible and was only undertaken in seven of our patients. Where synchronous femorodistal bypass was performed at the time of thrombectomy, one patient died postoperatively and two patients suffered further episodes of aortic graft occlusion during follow-up.

Death as a consequence of graft limb occlusion is usually associated with multiple synchronous procedures[2], particularly if they are in association with complicated forms of occlusion such as sepsis[3]. We have encountered no deaths so far after graft thrombectomy alone

It is inevitable, bearing in mind that 60–80 per cent of occlusions present with critical limb ischaemia[2,7,8], that major limb amputation will be necessary in some patients. Seven patients in this study (25 per cent) ultimately required amputation and this corresponds with the 14–32 per cent experience of others[2,7,10,13]. It is essential, therefore, that these patients are referred as early as possible for surgical intervention although, in our experience, the delay to referral has occasionally been as long as 1 year.

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Case report

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Innominate vein compression syndrome

A. Wurtz, P. Quandalle, L. Lemaitre* and Y. Robert*

*Clinique Chirurgicale Ouest and *Service de Radiologie Ouest, Hôpital Claude Huriez, Chu, 59037 Lille Cedex, France*

Correspondence to: Dr A. Wurtz

Superior vena caval syndrome is often caused by a malignant process. We report an unusual case due to intermittent compression of the left innominate vein (LIV) by the origins of the aortic arch vessels.

Case report

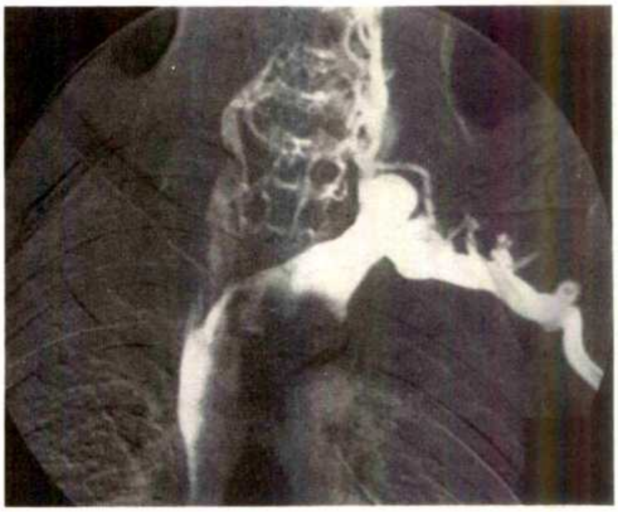
In November 1986, a 65-year-old hypertensive and atheromatous woman complained of left anterior chest wall oedema, predominately in the breast and extending to the left side of the neck. 'Unilateral superior vena caval syndrome'[1] was diagnosed and heparin treatment was started. The oedema decreased but venous dilatation over the left upper thorax persisted. Chest radiography was normal. Venography demonstrated a filling defect in the LIV, suggestive of thrombosis or intraluminal tumour, a prethrombotic dilatation, and opacification of the left vertebral vein and vertebral plexus (*Figure 1*). A computed tomographic (CT) scan, at the supra-aortic level, showed no tumour in the mediastinum and the LIV was clear and rather dilated. Because of these discordant findings, digital subtraction angiography was performed in the left posterior oblique position. It showed extrinsic compression of the LIV by the origins of the aortic arch vessels (*Figure 2*).

To explain this bizarre obstruction, dynamic phlebography, with injection of contrast medium into the axillary vein, was performed, which showed normal blood flow in the LIV at end inspiration and extrinsic compression during expiration, increasing during forced expiration. The main point of obstruction was the left subclavian artery (*Figure 3*).

An additional CT scan included anteroposterior measurements of the sternal–spinal distances. At the thoracic inlet, this diameter was 4 cm, corresponding to the lower limit in an average adult[2]. At the aortic arch level, the anteroposterior diameter was 9 cm at end inspiration and 6 cm at end expiration. A bolus injection of contrast medium at the supra-aortic level showed (1) moderate compression of the LIV arising from the brachiocephalic trunk and left carotid artery, independently of the left subclavian artery, and (2) elevation of the aortic arch during expiration with the brachiocephalic trunk and left carotid artery increasing their compression of the LIV, but the left subclavian artery causing a complete interruption of the venous blood flow (*Figure 4*).

We conclude that this unilateral superior vena caval syndrome was due to intermittent compression of the LIV by the supra-aortic trunks, mainly the left subclavian artery, during expiration.

The left superficial venous dilatation remains unchanged 22 months after the original presentation.



left innominate vein and opacification of the left vertebral vein and vertebral plexus

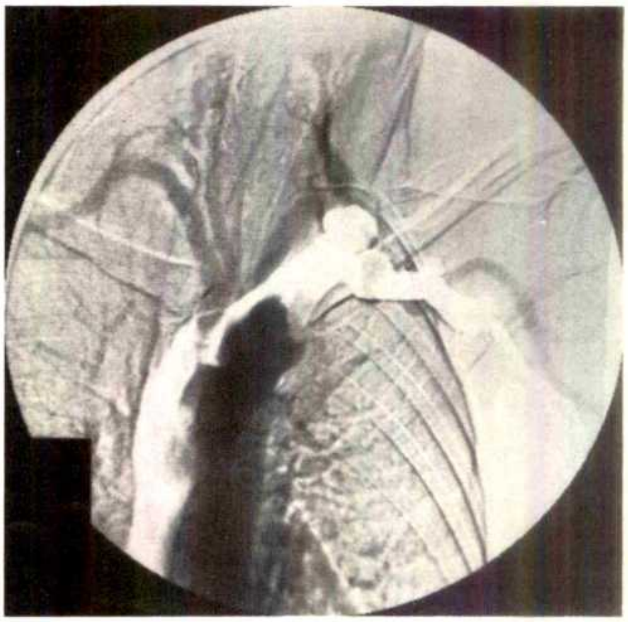


Figure 2 *Digital subtraction angiogram showing compression of the left innominate vein by the origins of the branches of the aortic arch*

Discussion

Aortic aneurysm is a common cause of benign superior vena caval syndrome, but extrinsic compression by a non-aneurysmal artery has not been reported[3,4], nor has unilateral superior vena caval syndrome[1]. However, some authors have previously described LIV compression by the aortic arch, leading to myelopathy, which was treated by partial resection

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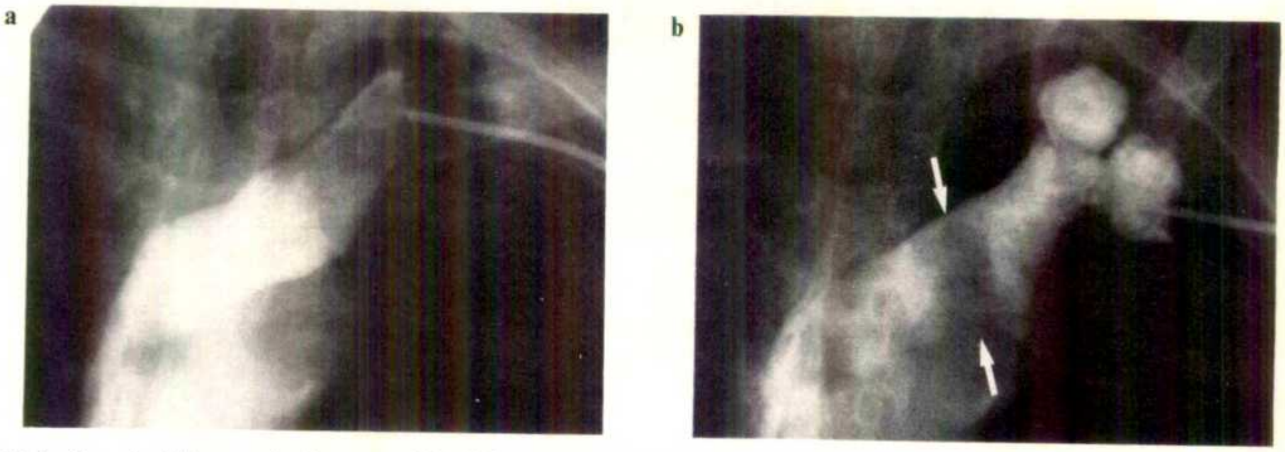

Figure 3 *Dynamic phlebogram showing* **a** *normal blood flow in the left innominate vein during inspiration and* **b** *extrinsic compression, mainly due to the left subclavian artery (arrows), during expiration*

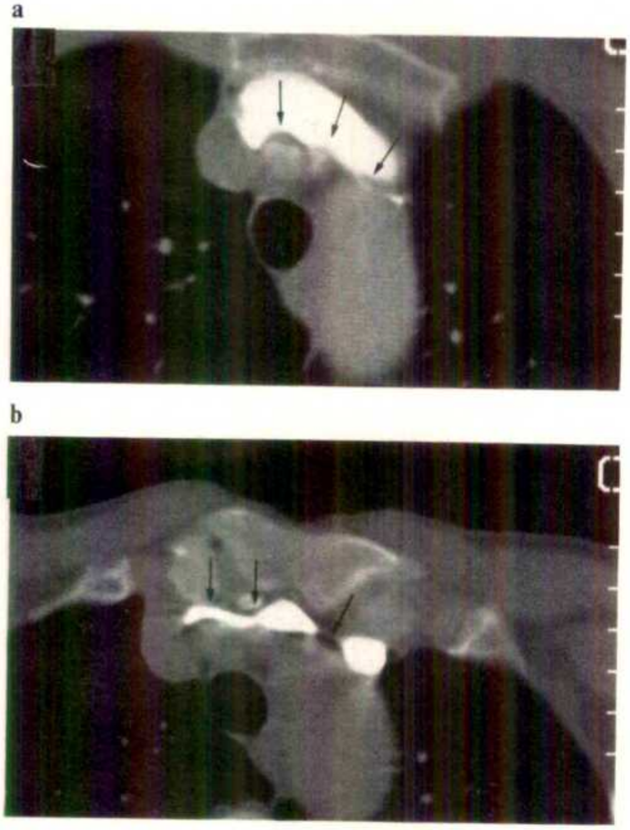

Figure 4 *Computed tomographic scan with bolus injection of contrast medium showing* **a** *moderate compression of the left innominate vein arising from the brachiocephalic trunk and left carotid artery and no compression from the left subclavian artery (vessels arrowed respectively from left to right) and* **b** *significant compression of the left innominate vein from the brachiocephalic trunk and left carotid artery with complete interruption of blood flow by the left subclavian artery (vessels arrowed respectively from left to right)*

of the anterior chest wall[5]. Such treatment seemed excessive for our patient.

Obstruction of the LIV by the left subclavian artery has never been described and the late development of symptoms may be due to arterial atheroma coupled with a narrow superior mediastinum. The remission of acute symptoms with heparin treatment was suggestive of initial venous thrombosis.

Compression of the left common iliac vein by the right common iliac artery due to an anatomical anomaly ('iliac compression syndrome' or 'Cockett's syndrome'[6,7]) is well known and acquired cases have been related to 'coiling' of an atheromatous iliac artery[8].

The case described here is a thoracic equivalent of Cockett's syndrome and so can be called 'innominate vein compression syndrome'.

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Role of venous elasticity in the development of varicose veins

H. Clarke,
S. R. G. Smith,
S. N. Vasdekis,
J. T. Hobbs and
A. N. Nicolaides

Irvine Laboratory for Cardiovascular Investigation and Research, Academic Surgical Unit, St. Mary's Hospital Medical School, London, UK

Correspondence to:
Professor A. N. Nicolaides
Vascular Surgery, 10th Floor,
Queen Elizabeth the Queen Mother
Wing, St. Mary's Hospital,
London W2 1NY, UK

A reduction in the 'elasticity' of the venous system has been proposed as a precursor of venous insufficiency, but the concept remains controversial. This study was designed to develop a method of assessing venous elasticity, and to use this method to investigate the aetiology of varicose veins. Simultaneous measurements of calf volume (determined using strain gauge plethysmography) and venous pressure (obtained via a dorsal foot vein) were made during venous occlusion plethysmography. The elastic modulus, K, defined as stress/strain when the veins are full, was calculated from the pressure/volume relationship. The elastic modulus was determined in 19 normal legs, 33 legs with superficial venous insufficiency, 16 legs with deep venous insufficiency, and 18 legs of a high risk group of volunteers or patients without varicose veins but with a strong history of factors associated with their development. The results showed a clear difference in elasticity between normal limbs and limbs with varicose veins, and also between normal limbs and high risk limbs. These results support the hypothesis that reduced elasticity has a role in the development of varicose veins and precedes the onset of valvular incompetence.

Keywords: Varicose veins, elasticity, plethysmography, venous pressure

Varicose veins are usually associated with dilatation and malfunctioning venous valves, which allow venous reflux to occur. Progression of the disease results in more pronounced dilatation and increased severity of reflux. The interaction between these two phenomena has not been determined and it is not clear whether the valvular incompetence occurs first and produces the dilatation, or vice versa.

A number of workers who have performed *in vitro* investigations into the pathology of varicose veins have suggested that the valvular incompetence associated with varicose veins arises following venous dilatation[1,2]. In contrast, *in vivo* investigation into the significance of the external iliac and femoral valves[3] has shown some association between a positive family history and the absence of these valves: also between impaired function of these valves and varicose veins.

Examination of the various theories about the development of varicose veins suggests that the weak wall theory is the most likely[4]. The manifestation of venous dilatation and associated mechanical weakening of the vein wall before the onset of valvular insufficiency has not been demonstrated.

Methods for assessing valvular function include the accepted standard of ambulatory venous pressure (AVP) measurements[5] and duplex Doppler scanning[6,7]. A similarly established method for assessing the function of the vein walls does not exist and until one becomes available the mechanisms underlying the development of primary varicose veins remain a matter for speculation[8].

The purpose of this study was to develop a method of assessing the vein wall function in order to investigate the role of venous elasticity in the development of varicose veins.

Patients and methods

Patient selection

In this study 19 volunteers (27 limbs) and 45 patients (59 limbs) referred from the vein clinic were investigated. The 86 limbs studied were classified into the four groups: normal, high risk, superficial vein incompetence, and deep vein incompetence, as shown in *Table 1*.

Limbs without varicose veins were classified as either normal or high risk, using the following criteria: family history of varicose veins, occupation involving standing, history of symptoms and signs associated with varicose veins, presence of reflux detected with Doppler ultrasound, and abnormal AVP recordings of >40 mmHg and RT_{90} (time required to achieve 90 per cent filling) <18 s.

If two or more of these criteria were present the limb was classified as being at high risk of developing varicose veins (18 limbs). Otherwise it was classified as normal (19 limbs).

The limbs with varicose veins or established venous disease were classified into two haemodynamic groups using AVP measurements and duplex scanning: superficial venous incompetence (33 limbs) and deep venous incompetence (16 limbs).

The measurement of elasticity

The experimental method used is shown in *Figure 1*. It combines standard strain gauge plethysmography[9,10] with venous pressure measurements. The patient was placed supine with one leg elevated 27 cm at the heel to allow the veins to empty. The knee was flexed and externally rotated and the thigh was supported to ensure that the leg was relaxed. Strain gauge plethysmography was performed using an electrically calibrated mercury in Silastic® (Dow Corning, Reading, UK) strain gauge (Perivein® JSI 0539/1, Janssen Pharmaceutical Ltd., Wantage, UK) placed around the calf at its maximum circumference, allowing percentage volume change to be determined. Measurements of venous pressure were obtained by inserting a 21-gauge butterfly needle into a vein on the dorsum of the foot. The strain gauge plethysmograph and pressure monitor were connected to a two-channel chart recorder, allowing simultaneous measurements of pressure and volume to be made.

The pressure:volume relationship of the lower limb venous system was obtained by inflating a 17-cm wide cuff placed around the thigh to 80 mmHg to occlude the venous outflow. Typical recordings of the

Table 1 *The number of limbs from volunteers and patients in the four groups*

	N	HR	SVI	DVI
Volunteer limbs	19	8	0	0
Patient limbs	0	10	33	16
Total	19	18	33	16

N, normal; HR, high risk; SVI, superficial vein incompetence; DVI, deep vein incompetence

Based on a paper presented to the Surgical Research Society, January 1988.

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subsequent changes in pressure and volume are shown in *Figure 2*. Simultaneous readings of pressure and volume were taken from the recordings every 15 s and plotted on a graph.

The change in pressure (ΔP) and the corresponding change in volume (ΔV) were measured in the linear, high pressure part of the pressure:volume curve. This linear region of the curve and the initial slope were extrapolated, as shown in *Figure 3*, to obtain the theoretical value of the initial volume V_0 pertaining to the changes in volume at high pressures. The elastic modulus, K, was calculated by substituting P, V, and V_0 in equation (1). This was converted to the International System of Units (millimeters of mercury to newtons per metre squared) using a standard conversion factor of 132·9.

$$K = \frac{\Delta P}{\Delta V / V_0} \qquad (1)$$

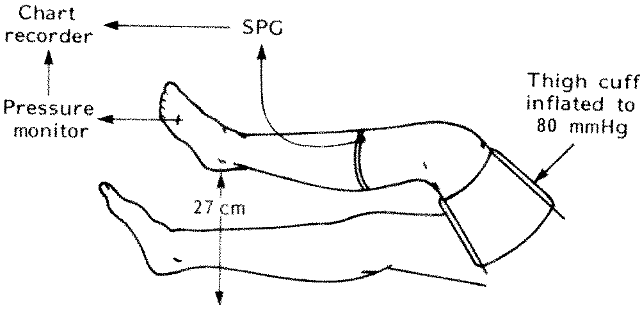

Figure 1 *The simultaneous measurement of pressure and volume with proximal occlusion. SPG, strain gauge plethysmograph*

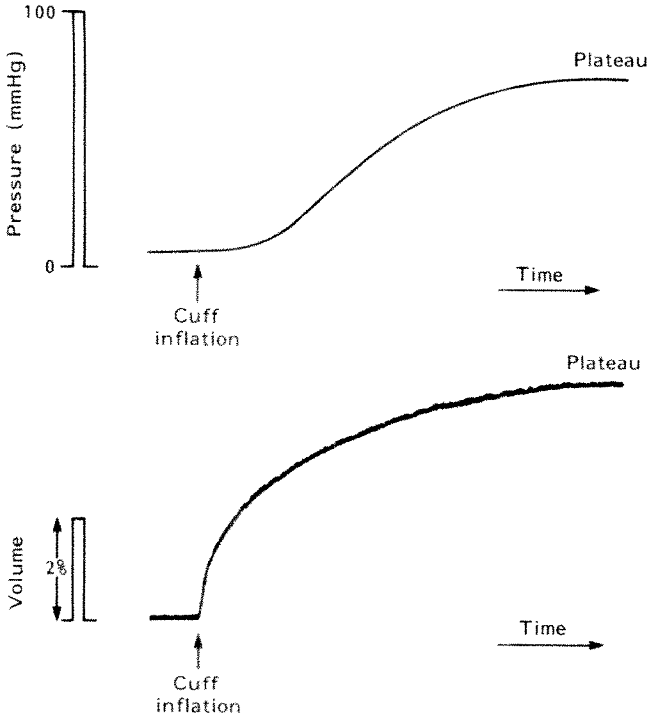

Figure 2 *Simultaneous recordings of pressure and volume obtained during venous occlusion*

This method of calculating the elastic modulus is inherently variable owing to the difficulty in determining the extent of the linear region of the curve and selecting the gradient. In order to standardize this a maximum and minimum gradient were obtained from each group and the mean value was used to calculate the elastic modulus. The maximum and minimum values were also used to determine the experimental variation (EV), which was then expressed as a coefficient of EV:

$$EV = \left[\frac{\sum (\mathrm{Max} + \mathrm{Min})^2}{2n}\right]^{\frac{1}{2}} \qquad (2)$$

$$\text{Coefficient of } EV = \frac{EV}{\bar{K}} \times 100 \qquad (3)$$

where n is the number of limbs, and $\bar{K}$ is the mean elastic modulus. This coefficient of experimental variation was calculated for each patient group.

Results

The number of limbs in each of the four groups and the results are summarized in *Table 2*. The elastic modulus, K, in individual limbs is shown in *Figure 4*, using a logarithmic scale because of the comparatively high values in the normal limbs. The elastic modulus is higher in the normal group than in either the high risk group or the two patient groups. There is no discernible difference in elasticity between the high risk group and the two patient groups. In the normal group there is a wide range in the measured elasticity but this group remains distinct from the other three groups.

Discussion

The method used to calculate the elastic modulus K is based on the relationship between the pressure/volume curve and the mechanisms of venous filling. At low pressures veins are empty and become collapsed. As the veins fill, two mechanisms control the venous filling[11]. Firstly, there is flexion of the walls as the

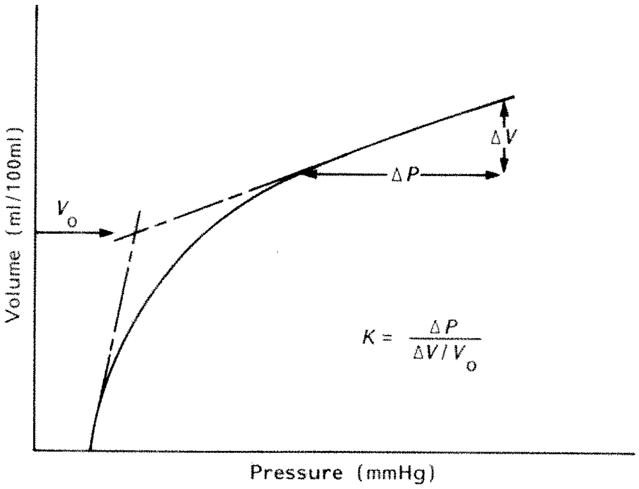

Figure 3 *Calculation of the elastic modulus, K, from the pressure/volume relationship. P, pressure; V, volume; V_0, initial volume*

Table 2 *The elastic modulus, K, determined in the four groups of patients and normal volunteers*

	N	HR	SVI	DVI
Number of limbs	19	18	33	16
Elastic modulus, K ($\times 10^4$ newtons m^{-2})				
Median	17·24	1·33	1·26	1·21
95% Tolerance levels	2·86–110·06	0·57–2·59	0·40–2·70	0·66–2·26
Coefficient of experimental variation (%)	20	19	25	25

N, normal; HR, high risk; SVI, superficial vein incompetence; DVI, deep vein incompetence

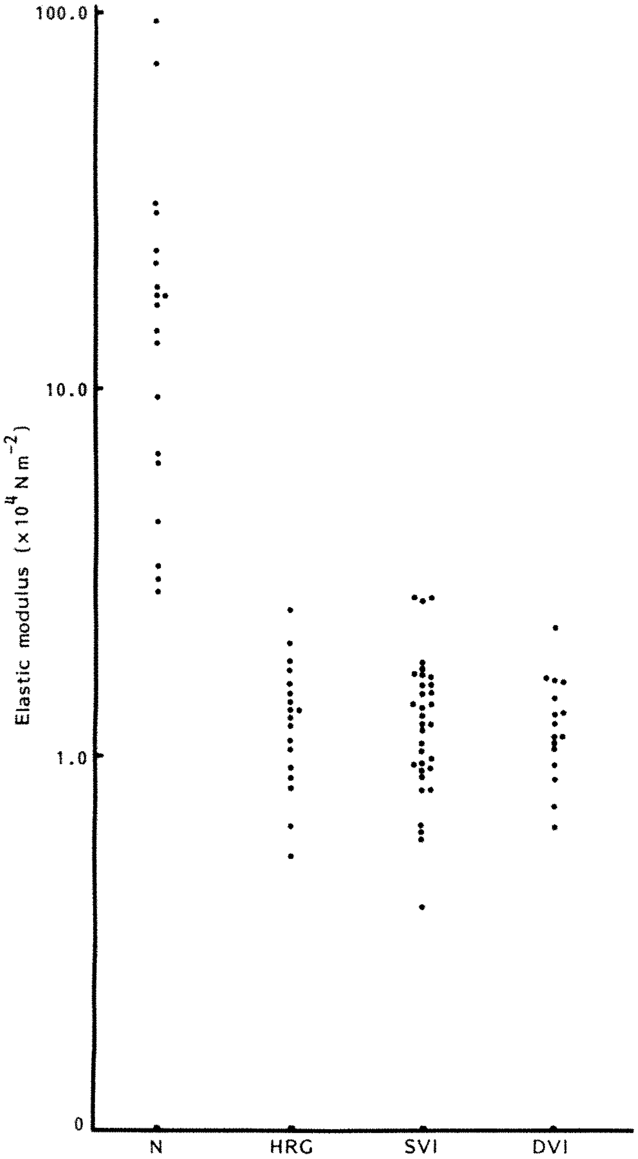

Figure 4 *The elastic modulus,* K, *for the four patient groups: N, normal; HR, high risk; SVI, superficial vein incompetence; DVI, deep vein incompetence*

collapsed veins fill to an elliptical and then circular cross-section; secondly, there is stretching of the vein wall which increases the circumference of the veins. The changes in vein configuration associated with venous filling and the pressure/volume relationship are shown in *Figure 5*. At low pressure flexion is the predominant mechanism whilst at high pressures stretching is predominant. In the initial phase filling occurs from a combination of both mechanisms.

Of these two mechanisms of venous filling it is stretching, rather than flexion, that is related to the dilatation and mechanical weakening of vein walls associated with venous disease. It is this aspect of the pressure/volume relationship that has been analysed, since the stretching of a vein is governed by its elasticity.

Elasticity is usually quantified in terms of an elastic modulus: K = stress/strain, where stress is the force per unit area, i.e. ΔP, and strain is the increase in volume per unit volume, i.e. $\Delta V/V_0$. Thus,

$$K = \frac{\Delta P}{\Delta V/V_0} \qquad (1)$$

The change in pressure and the change in volume were measured in the linear region of the curve where stretching predominates (*Figure 3*). Since K is a measure of vein stretching rather than flexion the theoretical initial volume, V_0, is the percentage volume measured when the veins have reached circular cross-section and are unstretched.

The measurements of the elastic modulus, K, indicate that the elasticity in normal limbs is higher than that in limbs with or at high risk of developing venous disease (*Figure 4*). The difference between normal limbs and limbs with established venous disease complies with theoretical expectations which predict that higher venous pressures weaken the vein walls with consequent deterioration of their mechanical properties. This difference also indicates that the measurement of the elastic modulus provides a means of assessing vein wall function in the lower limb.

The results indicate that this method cannot differentiate between the function of vein walls in the deep and superficial systems. This is because if any vein within the venous system has weaker functioning walls, filling of this vein swamps the measured changes in volume at the higher pressures, which results in a low measurement of elastic modulus. Thus the elasticity of the lower limb venous system is lowered by the behaviour of one vein, regardless of whether it is located in the deep or superficial system.

As the elastic modulus is obtained by measuring the gradient of the pressure/volume curve, the accuracy of each measurement depends partly on discrimination between the linear and the curved regions of the graph. In most cases this was clear and in consequence there was little difference between the maximum and minimum gradients, and the possible variation in K was low. In six cases, however, the linear region of the curve was not clear and there was a large difference between the maximum and minimum gradients. These cases were largely responsible for the high coefficient of maximum experimental variation.

The identification of patients in the early stages of venous disease is crucial to a study of the development of varicose veins. As most patients presenting in the vein clinic had more advanced disease, this posed a problem. Following recent work[12], the concept of finding venous disease in the normal contralateral limb of a patient with venous ulceration has been considered. Extending this idea it seems reasonable to expect that a number of the normal population might also have some degree of venous disease. This led us to the conclusion that there were two potential sources of patients in the early stages of the development of varicose veins. Firstly, there were the normal contralateral limbs of patients with unilateral disease and, secondly, there were volunteers from the so-called normal population.

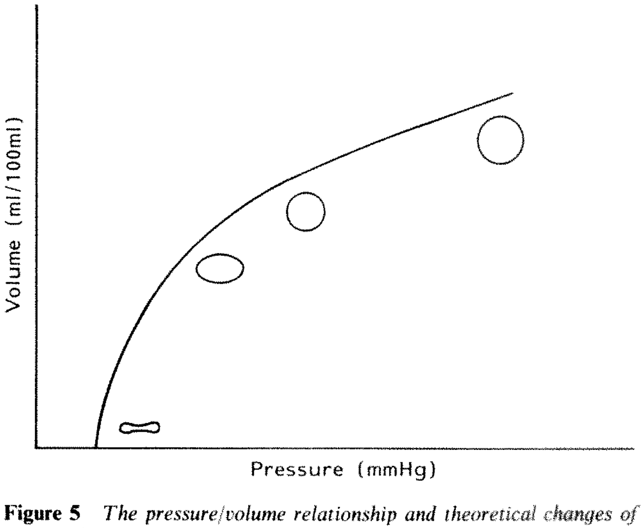

Figure 5 *The pressure/volume relationship and theoretical changes of vein configuration*

The separation of non-varicosed limbs into two groups of either normal limbs or limbs in the early stages of the development of venous disease was achieved by a combination of risk factors and measurements. As there is no evidence that the limbs classified as being in the early stages of disease will in fact develop varicose veins, these limbs have been defined as a high risk group.

The clear distinction between low risk normal limbs and limbs with established venous disease, and between low and high risk normal limbs suggests that the role of elasticity in the development of varicose veins precedes the valvular incompetence. This cannot be proved until follow-up data are obtained to establish the subsequent development of varicose veins in clinically normal high risk limbs with a low elastic modulus. The results of the present study, however, provide preliminary evidence in support of the weak wall theory of the development of varicose veins.

Acknowledgements

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Number and anatomical distribution of incompetent thigh perforating veins

K. Papadakis,
C. Christodoulou,
D. Christopoulos,
J. Hobbs,
G. M. Malouf,
M. Grigg,
A. Irvine and
A. Nicolaides

Irvine Laboratory for Cardiovascular Investigation and Research, Vascular Unit, Academic Surgical Unit and Department of Radiology, St. Mary's Hospital Medical School, London, UK

Correspondence to:
Professor A. N. Nicolaides,
Academic Surgical Unit, St. Mary's
Hospital Medical School,
Praed Street, London W2 1PG, UK

Although incompetent thigh perforating veins are considered to be a common cause of recurrence of varicose veins after high saphenous ligation, the number and distribution of such incompetent veins have not been reported. The aim of the study was to determine the number and anatomical distribution of incompetent thigh perforating veins. Sixty-five limbs in 48 patients with varicose veins who were found to have incompetent thigh perforating veins on ascending deep to superficial venography were studied. In 80 per cent of patients one incompetent thigh perforating vein was found and in 20 per cent more than one was found. Concomitant incompetent calf perforating veins were found in 92 per cent of the limbs studied. The incompetent thigh perforating veins were found to occur anywhere in the thigh, from the upper edge of the patella to a few centimetres below the saphenofemoral junction. The majority (71 per cent) were found in the middle third of the thigh. All incompetent thigh perforating veins were communicating with the long saphenous vein, including those in five patients with incomplete stripping. The surgeon should be aware of incompetent thigh perforating veins which may be multiple and occur at any site on the medial aspect of the thigh.

Keywords: Varicose veins, incompetent perforating veins, anatomical distribution

There is an increased awareness that incompetent thigh perforating veins are a common cause of postoperative recurrence of varicose veins[1,2] and that in some patients they may even be a cause of varicose ulceration[3,4]. Despite this the sites and number of incompetent thigh perforating veins have not been reported, in marked contrast to the relatively large number of studies on incompetent calf perforating veins[5–8]. A search of the literature has revealed publications based on anatomical and surgical dissections[9–12] describing the anatomy of the normal perforating veins in the thigh rather than the distribution of the incompetent veins. Because of the surgical implications the purpose of our study was to determine the sites, distribution and number of incompetent thigh perforating veins in patients shown to have such incompetent veins by venography.

Patients and materials

Patients

Forty-eight patients who presented with varicose veins in 65 legs and who were found to have incompetent thigh perforating veins on ascending deep to superficial venography have been included in this study. Venography was part of the routine investigation of patients with varicose veins in whom, because of the clinical examination, tourniquet tests and Doppler ultrasound examination, incompetent thigh perforating veins were suspected. Patients whose venograms did not confirm the presence of such perforating veins were excluded from the study.

Forty-two of the 48 patients had had a previous operation for their varicose veins; 37 (50 legs) had ligation of the saphenofemoral junction without stripping and five (six legs) had ligation with stripping of the long saphenous vein.

None of the patients had a history of deep venous thrombosis, and reflux was not detected in the popliteal vein by Doppler ultrasound[13,14] or venography although five had lower leg ulceration. *Table 1* summarizes the clinical information of the patients.

Technique of venography

A vein on the dorsum of the foot was cannulated using a butterfly needle (21G) through which meglumine sodium ioxalate 320 (Hexabrix 320®, May and Baker, Dagenham, UK)) was injected. A narrow (2·5 cm) pneumatic cuff was applied to the ankle so that the contrast medium was directed into the deep veins. The radiographic table was tilted 60° to the horizontal (head up) and the progress of the contrast medium was followed using an image intensifier.

The presence of incompetent calf perforating veins, as indicated by the flow of contrast medium from the deep to the superficial veins, was noted and films were taken. When contrast medium entered the lower popliteal vein, the competence of its valves was tested by manually compressing the calf muscles and following the direction of flow of the column of blood and contrast medium. Retrograde flow on release of the compression indicated popliteal reflux; flow only proximally with absence of reflux confirmed a competent popliteal system (patients with popliteal reflux were excluded from the study). With further injection of contrast medium and the use of Valsalva's manoeuvre the superficial femoral vein and incompetent thigh perforating veins were visualized: contrast medium was seen to flow from the superficial femoral vein through the perforating veins to the superficial system, either the long saphenous vein or a tributary. A special ruler with radio-opaque markings was positioned on the medial aspect of the limb with zero at the level of the knee joint (under direct fluoroscopy) so that the level of a perforating vein in terms of its distance from the knee could be

Table 1 *Clinical data of the 48 patients (65 limbs) included in the study*

	Number of patients	Number of limbs
Men (age: mean ± s.d. 54 ± 11)	17	24
Women (age: mean ± s.d. 47 ± 11)	31	41
Previous operation (time since operation in years: mean ± s.d. 9·5 ± 6·5)	42	56
Previous high saphenous ligation only	37	50
Previous high saphenous ligation and stripping of the long saphenous	5	6
Reflux detected in the region of the saphenofemoral junction on venography	15	21
Ulceration	5	5
History of deep venous thrombosis	0	0
Deep venous insufficiency (reflux)	0	0
History of superficial thrombophlebitis	5	7
Previous injection sclerotherapy	9	12

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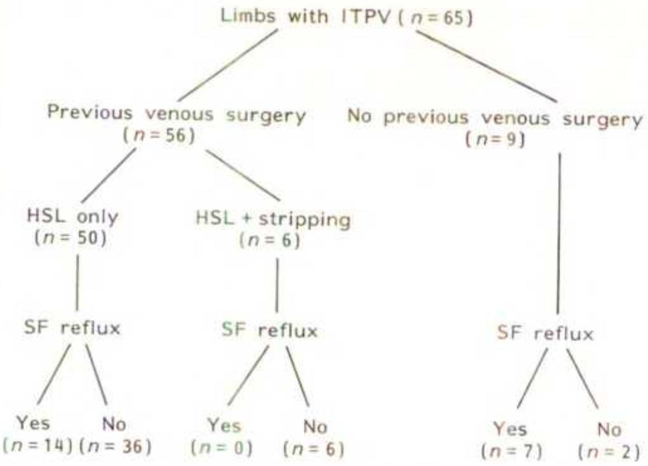

Figure 1 *The incidence of high saphenous ligation (HSL), stripping of the long saphenous vein and reflux at the saphenofemoral (SF) junction in the 65 limbs with incompetent thigh perforating veins (ITPV) included in this study*

attained. Finally, when contrast medium reached the common femoral vein the calf muscles were compressed, again in order to detect the presence or absence of reflux at the saphenofemoral junction immediately after release of the compression.

Results

Of the 65 limbs with incompetent thigh perforating veins studied, 56 had undergone a previous operation for varicosities (*Figure 1*). Fifty had a high saphenous ligation without stripping and six with stripping of the long saphenous vein. The incidence of reflux (recurrent or persisting) in the region of the saphenofemoral junction demonstrated by Doppler ultrasound and venography is also shown in *Figure 1*. It was present in a total of 21 (32 per cent) limbs.

The number of incompetent thigh perforating veins was one in 52 (80 per cent), two in 12 (18·5 per cent) and three in one (1·5 per cent) of the 65 limbs. Concomitant incompetent calf perforating veins were present in 60 (92 per cent) of the 65 limbs studied. An example of two incompetent thigh perforating veins is shown in *Figure 2*.

The distribution of the incompetent thigh perforating veins measured in centimetres from the knee joint is shown in *Figure 3*. Because the length of the femur and thigh vary according to the height of the patient, the results have been normalized by expressing the site of each incompetent perforating vein as a percentage of the length of the femur. The knee joint was zero and greater trochanter was 100 per cent (*Figure 4*).

The distribution per quarter of the femur or per third of the thigh (whole thigh: 0–75 per cent) is shown in *Figure 5*. It can be seen that 19 per cent are in the lower third, 71 per cent are in the middle third and 10 per cent are in the upper third of the thigh.

Table 2 shows the time to recurrence of varicose veins in relation to the original operation: high saphenous ligation only or high saphenous ligation with stripping.

Discussion

Sherman[9] first studied thigh incompetent perforating veins. His interest was aroused by a high 'recurrence' rate of varicosities (46 per cent), many attributed to thigh incompetent perforating veins in patients he had treated by flush ligation of the saphenofemoral junction and its tributaries followed by the injection of a sclerosing solution into the varices. He drew attention to the numerous anatomical variations and stated that although perforating incompetent veins could be found anywhere between the knee and the groin there were four constant sites: (a) the mid-Hunter canal vein, (b) the subsartorial vein, (c) the lower subsartorial vein, and (d) a perforating vein from the long saphenous to the femoral vein 6–8 cm below the saphenofemoral junction.

Dodd[3] also studied 52 limbs with varices for the presence of thigh incompetent perforating veins by exposing the Hunterian canal at operation. In 12 limbs the varices had not been treated earlier, but in the remaining 40 the varices had 'persisted' despite a previous operation. The number of incompetent perforating veins found were one in ten patients, two in another ten patients and three in one patient. The lowest

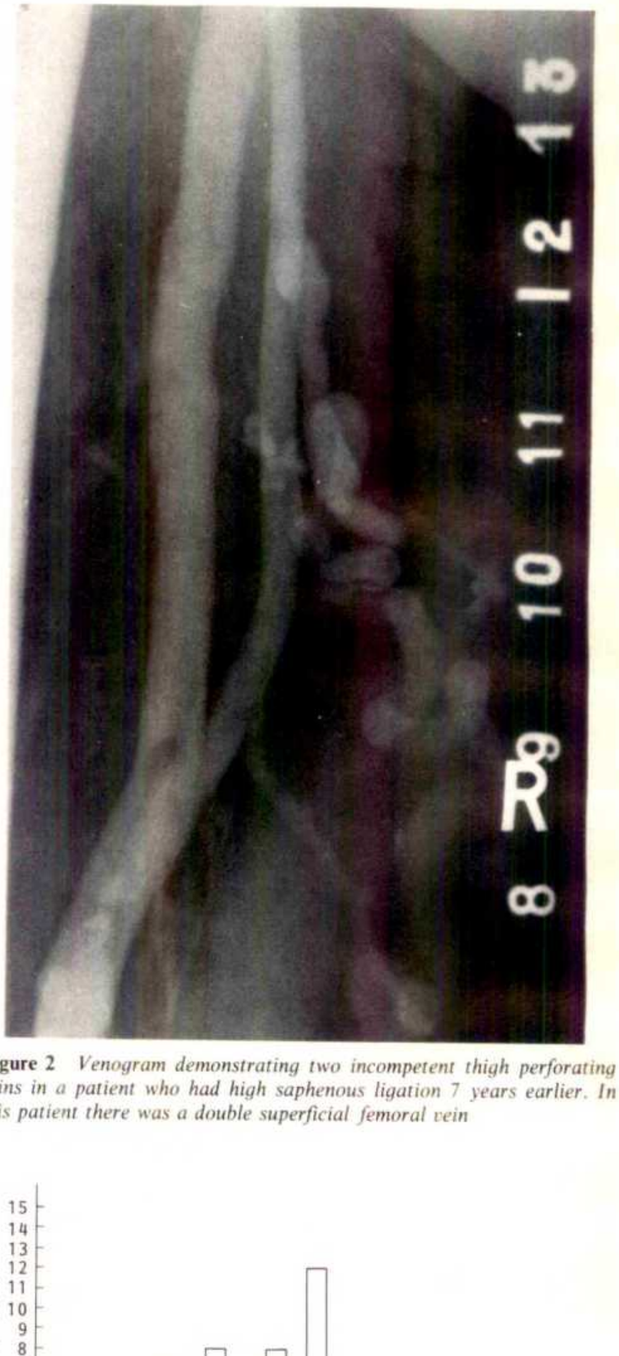

Figure 2 *Venogram demonstrating two incompetent thigh perforating veins in a patient who had high saphenous ligation 7 years earlier. In this patient there was a double superficial femoral vein*

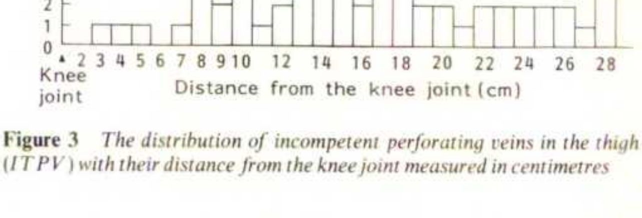

Figure 3 *The distribution of incompetent perforating veins in the thigh (ITPV) with their distance from the knee joint measured in centimetres*

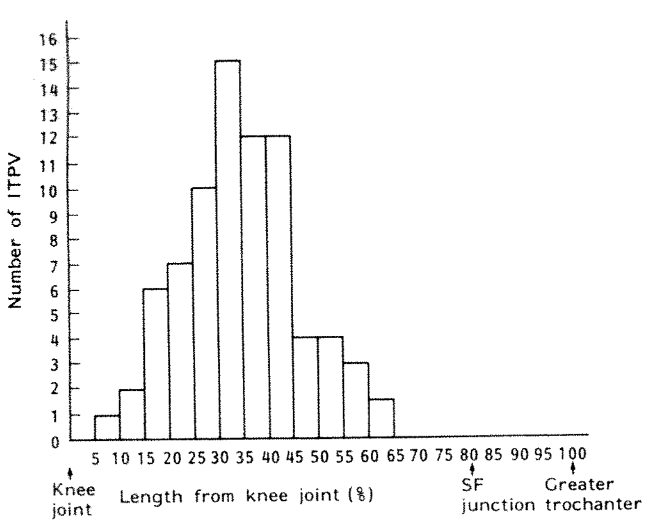

Figure 4 *The distribution of incompetent perforating veins in the thigh (ITPV) with their distance from the knee joint expressed as a percentage of the length of the femur. SF, saphenofemoral*

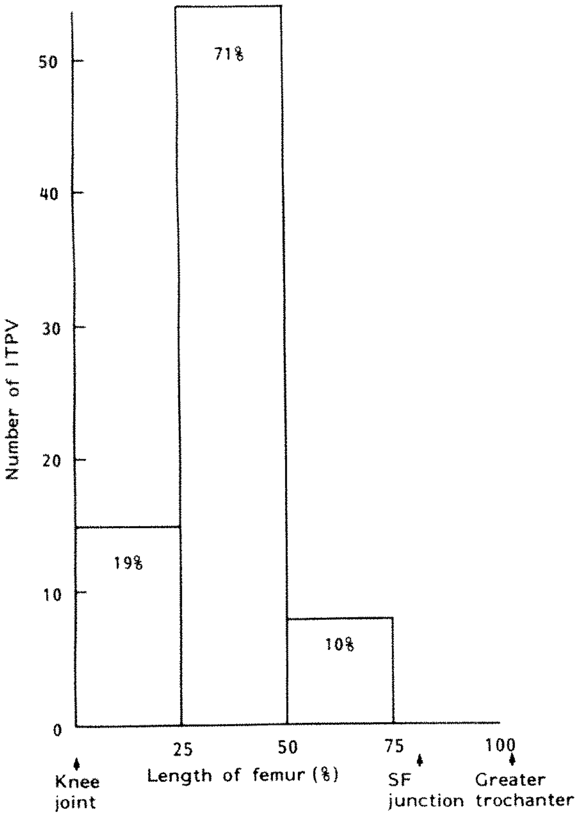

Figure 5 *The distribution of incompetent perforating veins in the thigh (ITPV) in each quarter of the femur or third of the thigh (thigh: 0–75 per cent). SF, saphenofemoral*

of the three perforating veins exposed in the canal was the one most commonly found to be incompetent. Dodd concluded that 'varicose communicating veins passing into the superficial femoral vein through Hunter's canal are often missed in diagnosing varicose veins, and are a cause of persistent varices after operation'[3].

From a large series of anatomical dissections van Limborgh *et al.*[11] and van Limborgh and Hage[12] classified the thigh performing veins into three groups: medial, lateral and posterior. They emphasized that the medial group is surgically the most important because of its connections to the long saphenous vein and the frequency of incompetence.

Because of the wide variation in the position of the thigh incompetent perforating veins and the need to avoid a long incision along the thigh as described by Dodd[3], Doran and Barkat[15] advocated deep to superficial venography to localize them. They claimed that the identification of the veins and their site saved many patients from unnecessary or unsuccessful operations.

The high incidence (39 per cent) of incompetent thigh perforating veins in patients with recurrent varicose veins (38 limbs) has been confirmed recently by varicography[1]. Sutton and Darke[4] have emphasized the need to strip the long saphenous vein in the thigh in order to disconnect such perforating veins from the superficial system. In our study all incompetent thigh perforating veins communicated with the long saphenous vein; this included the five patients who had incomplete stripping presumably because a large branch rather than the main trunk was stripped.

The aim of our study was to determine the number and anatomical distribution of the incompetent perforating veins along the thigh. Previous similar studies[3,9–11] have used clinical identification and surgical dissection rather than deep to superficial venography to identify these veins. Thigh incompetent perforating veins can be demonstrated using Valsalva's manoeuvre during ascending venography with an accuracy of 80 per cent, as judged by surgical exploration[16]. It should be pointed out that the effectiveness of the Valsalva manoeuvre becomes distally progressively less and it is possible that in some patients the number of incompetent perforating veins has been underestimated.

Our results indicate that incompetent thigh perforating veins can exist anywhere along the course of the long saphenous vein in the thigh, from the upper edge of the patella to a few centimetres below the saphenofemoral junction, although 70 per cent can be found along its middle third, an area that corresponds anatomically with the adductor canal. In 20 per cent of our patients there was more than one incompetent thigh perforating vein and this finding has important surgical implications.

The coexistence of 92 per cent of incompetent calf perforating veins suggests that in these patients varicose veins were the result of a more generalized disease rather than of just a few localized incompetent sites.

A number of questions remained unanswered. Were these incompetent thigh perforating veins present at the time of the first operation or did they occur afterwards? Would stripping of the long saphenous vein have prevented a recurrence in the majority of these limbs? The early recurrences (from months to 3 years) in seven limbs suggest that at least in some patients the incompetent perforating veins could have been present at the time of the original operation. The late recurrences (10–16 years) in 12 limbs suggest that many perforating veins become incompetent a long time after the operation (*Table 2*). After stripping, incompetent thigh perforating veins associated with recurrent varices were found 13–34 years after the operation (13, 18, 21, 23, 28 and 34 years in six limbs). Although these data support the rationale that stripping the long saphenous vein in the thigh[4,17,18] will prevent early recurrence associated with incompetent thigh perforating veins, the definitive answer can only be obtained from prospective studies. In the meantime, the surgeon should be aware of the possible

Table 2 *Time of recurrence of varicose veins in relation to the original operation*

	Recurrence time (years)			
	0–3	4–9	10–16	>16
Group A (HSL only)	7	18	12	0
Group B (HSL + stripping)	0	0	1	4

HSL, high saphenous ligation

presence of incompetent thigh perforating veins which may be multiple and occur at any level along the whole length of the medial aspect of the thigh.

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Lower limb vein trauma: a long-term clinical and physiological assessment

The aim of this study was to assess the long-term clinical and physiological sequelae of lower limb venous trauma in a civilian practice. Twenty-six patients who had undergone surgery for lower limb venous trauma (median elapsed time 19·5 months) underwent assessment. Injuries had been sustained to the external iliac, common femoral, superficial femoral and popliteal veins in two, four, nine and eleven limbs respectively. Using clinical assessment, photoplethysmography recovery time, the presence of popliteal reflux and venographic evidence of thrombosis, the final outcome was graded as good, fair or poor. Fourteen patients had pedal oedema, including two with a postphlebitic limb. The overall photoplethysmography recovery time (mean and s.d.) was 20·6 (8·7) s in the injured and 32·1 (6·7) s in the non-injured limbs (P = 0·002). Patients with a venographically occluded vein had a shorter photoplethysmography recovery time than those in whom the vein was patent (13·4 (5·6) versus *21·6 (8·7) s; P = 0·07). Popliteal reflux was present in 12 injured limbs. Seven of 12 venograms performed on limbs with a vein repair had evidence of previous thrombosis. Vein ligation carried considerable morbidity and all end-to-end anastomoses initially failed. In retrospect, saphenous vein grafts were too narrow for the recipient veins and panel grafts might have been more appropriate. Overall 11 of 26 patients (42 per cent) had a poor result. The repair of choice is a saphenous vein patch for lesser injuries and a saphenous panel graft for major injuries. Vein ligation should be avoided unless another life-threatening injury demands priority.*

Keywords: Trauma, lower limb, venous surgery, morbidity

R. J. Aitken*, P. J. Matley and E. J. Immelman

The Vascular Laboratory, The Department of Surgery, The University of Cape Town and Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa

Correspondence to:
Professor E. J. Immelman

The management of injuries to the deep veins of the lower limb remains a challenge. The morbidity of routine vein ligation was appreciated only after Rich *et al.* published their analyses of the Vietnam Vascular Register[1–3] and, although most reports continue to advocate repair, some recent publications have reported minimal morbidity after vein ligation[4–6]. It has been suggested that this may be explained, in part, by the nature of the injury, for earlier publications predominantly report combat injuries[1–3,7] where the circumstances differ substantially from those in civilian practice[4–6,8–10]. A further explanation may be the lack of good follow-up data which is an acknowledged shortcoming in all these studies. This is a significant omission as the long elapsed period required for the development of the postphlebitic limb is well documented[11]. Follow-up data have not been provided in some studies[9,10,12–14] and are limited to the short term in others[8,15–17]. Many of the follow-up data available have been obtained indirectly (e.g. postal questionnaire[2,3]) and few patients have been personally assessed[5]. No study has attempted to assess physiological venous function although venography has been performed in some patients[4]. The aim of the present study was to assess long-term clinical and physiological functions after lower limb venous trauma in a civilian practice.

Patients and methods

The hospital records of patients admitted during 1980–87, inclusive, with a lower limb vascular injury were reviewed and patients who sustained a vein injury (excluding saphenous vein injury alone) were invited to attend the vascular laboratory. Details recorded included the patient's age, sex, the elapsed time between injury and assessment, mechanism of injury, the vessel injured, the repair undertaken and the use of adjuvant procedures such as temporary shunting, fasciotomy or postoperative anticoagulation. After clinical assessment the patients underwent photoplethysmography[18], popliteal and femoral vein Doppler reflux studies[19] and, whenever possible, contrast venography of the injured limb performed after the method of Rabinov and Paulin[20]. The patient's non-injured limb was used as his own control.

Using these results the outcome of the injury was classified as good, fair or poor, and when the category was uncertain the better result was assumed (*Table 1*). If a surgically correctable lesion was identified the patient was offered reconstructive surgery[1]. Statistical analysis was by the Student's *t* test. The study was approved by the University of Cape Town Ethical Trials Committee and the patients undergoing venography gave informed consent.

Results

We were able to contact 26 of 48 patients who had undergone surgery for a lower limb vein injury during the study period; all attended the vascular laboratory and they form the basis of this report (*Table 2*). Five of the remaining 22 patients could not be assessed; two patients died in the early postoperative period from associated injuries and two patients required amputations for extensive soft tissue injuries. The popliteal vein in another patient was noted to be thrombosed when the

Table 1 *Assessment criteria of final outcome*

	Good	Fair	Poor
Photoplethysmography	> 21 s	Abnormal, > 17 s	Abnormal, < 17 s
Reflux	Negative	Positive	Positive
Venogram	Patent	Patent	Thrombosed
Oedema	Nil	Minimal	Severe

**Present address: The University Department of Surgery, The Royal Infirmary, Edinburgh EH9 3YW, UK*

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Table 2 *Injured vessels*

Vessels	Artery and vein	Vein only
External iliac	1	1
Common femoral	2	2
Superficial femoral	7	2
Popliteal	9	2
Total	19	7

Table 3 *Method of repair*

	Injured vein				
	External iliac	Common femoral	Superficial femoral	Popliteal	Total
Ligation	1		2	3	6
Lateral suture	1	2	1	4	8
Vein patch		1	1	1	3
End-to-end anastomosis			2	1	3
Interposition saphenous vein		1	2	2	5
Panel graft			1		1
Total	2	4	9	11	26

Table 4 *The incidence of clinical oedema for each method of repair*

	Clinical oedema	No clinical oedema
Ligation	5	1
Lateral suture	5	3
Vein patch	1	2
End-to-end anastomosis	1	2
Interposition saphenous graft	2	3
Panel graft		1
Total	14	12

popliteal artery required re-exploration 10 days after an end-to-end repair of both the vein and artery.

The median age at the time of surgery was 26 years (range 11–51 years) and the median elapsed time from injury to assessment was 19·5 months (range 0·5–66 months). Twenty-five patients were men and had injuries sustained by gunshot (15 patients), stab (6 patients) or major blunt trauma (4 patients). The single woman had an iatrogenic injury during varicose vein surgery.

The repairs undertaken are detailed in *Table 3*. Two patients had a temporary arterial shunt inserted while the vein was repaired and 12 patients, of whom only one had an isolated vein injury, required an adjuvant fasciotomy. In the immediate postoperative period five patients received postoperative subcutaneous heparin 5000 units, 8- or 12-hourly, and one received low molecular weight dextran.

Two of three patients in whom the popliteal vein was ligated required urgent re-exploration within 12 h of surgery for severe limb-threatening oedema[2]. One then had an end-to-end anastomosis of the vein and the other a fasciotomy only. Two years later the latter patient required vein reconstruction for a chronically swollen leg. Clinical oedema also developed in both the superficial femoral veins and the single external iliac vein that had been ligated (*Tables 3* and *4*). On examination, 14 patients had dependent pedal oedema (*Table 4*) of whom 13 had abnormal venous function. Two of three patients in whom the popliteal vein had been ligated had an established postphlebitic limb. Twelve patients had no pedal oedema but four had abnormal venous function and continue to be observed.

Photoplethysmography was performed in all 26 patients. An abnormal photoplethysmogram upon which no meaningful interpretation could be performed was recorded in three patients in whom the vein had been repaired (three injured limbs and two non-injured limbs). The overall photoplethysmography recovery time (mean and s.d.) was 20·6 (8·7) s in the 23 injured limbs and 32·1 (6·7) s in the 24 non-injured limbs ($P = 0{\cdot}002$). The photoplethysmography recovery times of those having venography are shown in *Figure 1*. Popliteal venous reflux was found in 12 injured limbs. None of the non-injured (control) limbs had oedema or Doppler reflux.

Ascending venography was performed in 17 patients. The vein was occluded in 11 patients (*Figure 1*); the vein had been ligated in six and thrombosed in five. Nine of the 11 limbs shown on venography to have an occluded vein had oedema with abnormal function. Two of the 11 limbs were without oedema: one had abnormal function and one normal function. Extensive venous collaterals were found in all six limbs in which the vein had been ligated and five had developed oedema which was associated with abnormal function (*Figure 2*). The vein was patent in six patients. Five had no evidence of oedema, but three had associated abnormal function, and the sixth limb had a patent vein with oedema and abnormal function. Twelve limbs that had undergone vein repair had a venogram and seven (58 per cent) had evidence of previous thrombosis.

The 17 patients who underwent venography were subdivided in two groups depending on whether the deep veins were patent (six patients) or thrombosed (11 patients; *Figure 1*). The three patients with abnormal photoplethysmography underwent venography and although the non-injured vein was normal the injured vein had thrombosed in all three. Thus in the thrombosed group only eight injured and nine non-injured limbs were available for assessment. The photoplethysmography recovery time (mean and s.d.) in the injured limbs was significantly shorter than in the non-injured limbs in both those with a thrombosed vein (13·4 (5·6) *versus* 32·2 (10·6) s, $P = 0{\cdot}001$) and those with a patent vein (21·6 (8·7) *versus* 35·0 (4·5) s, $P = 0{\cdot}004$; *Figure 1*). The photoplethysmography recovery time in the injured limbs with a thrombosed vein on venography was shorter than in those with a patent vein but this difference was not significant (13·4 (5·6) *versus* 21·6 (8·7) s, $P = 0{\cdot}07$).

Our assessment of the final outcome is shown in *Table 5*. One patient with a poor/fair outcome was placed in the fair group.

Discussion

This study has two principal conclusions. Firstly, that in the long term 58 per cent of the repaired veins thrombosed and, secondly, even after successful repair, as demonstrated by a patent vein on venography, there may be serious physiological

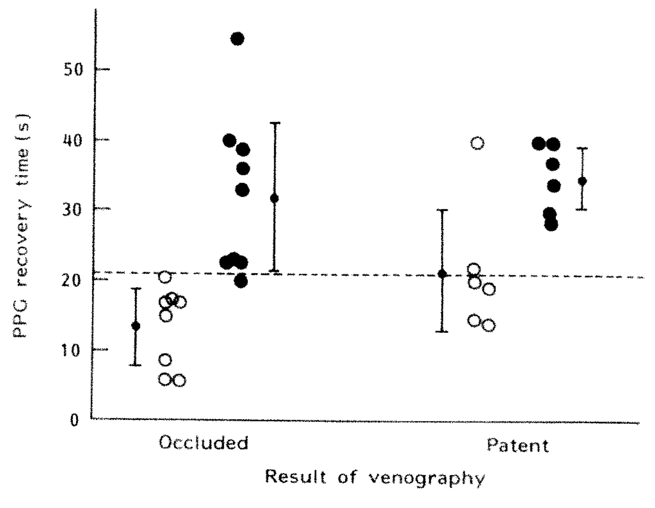

Figure 1 *The photoplethysmography (PPG) recovery time (mean and s.d.) in patients with occluded or patent veins at venography for both the injured (○) and non-injured (●) limb*

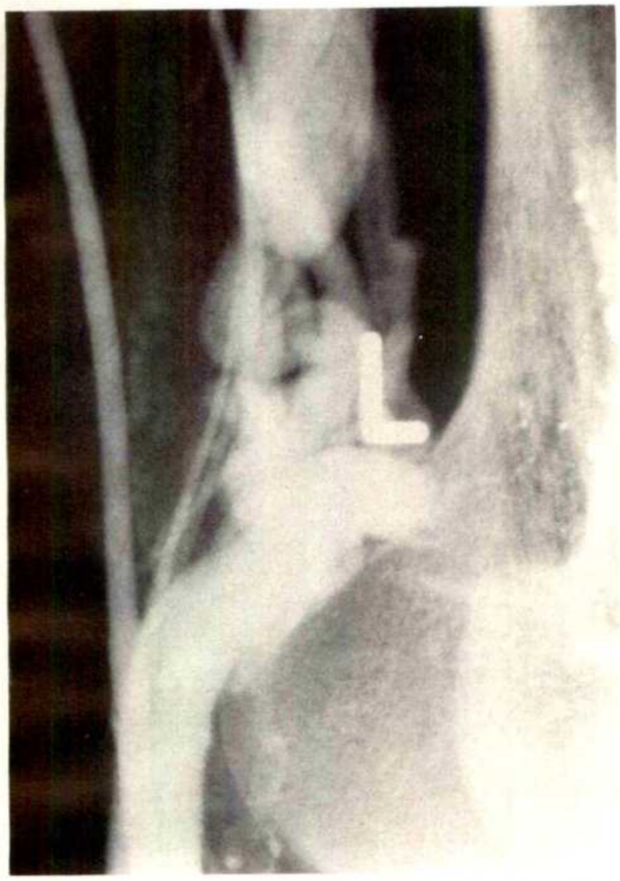

Figure 2 *Venogram of a popliteal vein after ligation. Extensive collaterals had developed but there was gross clinical oedema and venous reflux, and the photoplethysmography recovery time was 17 s*

Table 5 *Assessment of outcome*

	Good	Fair	Poor
Ligation	1	1	4
Lateral repair	3	2	3
Vein patch	2		1
End-to-end anastomosis		1	2
Interposition saphenous vein	2	2	1
Panel graft		1	
Total	8	7	11

impairment of venous function when assessed by photoplethysmography. Patients thus affected, who are often young men, may then be at risk of subsequent development of a postphlebitic limb, an essentially incurable chronic disability that causes much social, economic and physical hardship[21]. This study has also confirmed the harmful consequences of popliteal vein ligation and suggests that ligation of the proximal lower limb veins is associated with appreciable clinical morbidity and abnormal physiological function.

These new observations are important because previous studies, which have not always concluded that repair is necessary[4–6], arrived at their conclusions without the benefit of any follow-up[9,10,13,14] or after only short follow-up[7,15–17] unaided by either venographic or physiological assessment[4,5]. We believe that adequate assessment in either the short or long term can be obtained only if it includes both venography to determine patency and physiological tests to measure function. Laboratory evaluation may identify those patients likely to develop a postphlebitic limb at an earlier stage and permit careful follow-up. Although photoplethysmography is simple, non-invasive and easy to repeat, the muscle pump may not be normal following fasciotomy and we are currently assessing photoplethysmography after fasciotomy.

The surgeon has two goals when approaching vein injuries. The first is to ensure the limb survives the acute trauma and the second is to restore long-term venous function. That individual, injured lower limb veins can be ligated without immediate serious sequelae has never been denied but what has been debated is the wisdom of adopting ligation as the preferred strategy. Limb loss has been reported following popliteal vein ligation[1,9,13] and we believe the evidence in the literature, supported by this study, demonstrates that popliteal vein ligation is not acceptable unless an associated life-threatening injury demands priority. The acute consequences of proximal vein ligation appear to be less serious, presumably due to the development of more extensive collaterals, but this has not been adequately studied. In the present study, patients in whom the superficial femoral vein (two patients) or the external iliac vein (one patient) was ligated had oedema and abnormal function tests.

The only disadvantage of venous repair is the time required to execute the repair and possibly the only indications for venous ligation are complex lacerations or associated injuries that require priority. Those who advocate vein ligation argue that early thrombosis frequently occurs following vein repair and that within a few days sufficient collaterals will have developed to ensure limb survival[7,16]. We have shown that, even after the development of extensive collaterals, vein function generally remains abnormal even though the immediate catastrophe of limb-threatening oedema or venous gangrene is avoided. Combined arterial and venous injuries are more serious than venous injuries alone[1,16,22] and the normal revascularization oedema that follows limb ischaemia must be aggravated when the vein is ligated. Although it has been suggested that if the vein thromboses after a repair the risk of a subsequent pulmonary embolus is increased, there is little evidence to support this.

To reduce the 60 per cent thrombosis rate in this and other studies[17,22], perioperative care must be meticulous. Minor injuries may be repaired by lateral venorrhaphy but in the present series venography revealed that the lumen was often

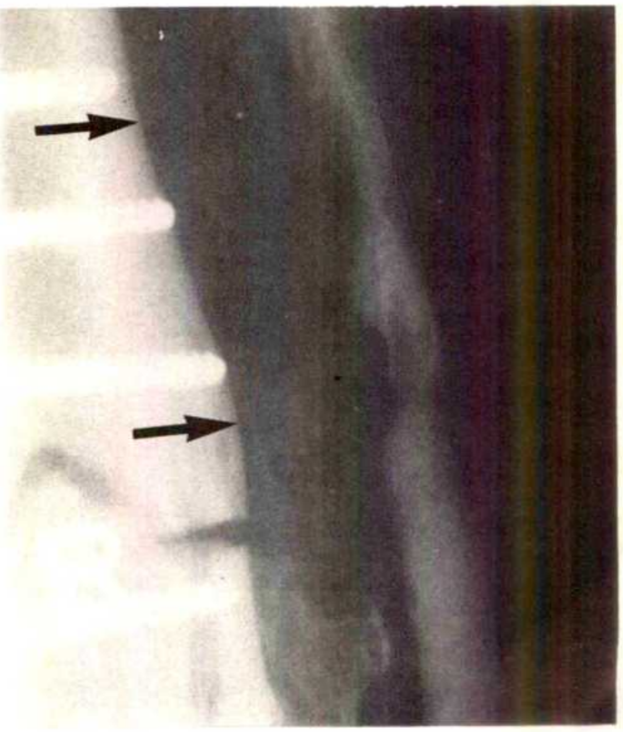

Figure 3 *Venogram of a superficial femoral vein repaired with a panel graft. There were no collaterals and the patient remains asymptomatic*

narrowed by this technique and if there has been any tissue loss a vein patch should be used. In all major injuries a saphenous vein graft from the opposite limb should be harvested but, in our experience and that of others, the donor vein is often too narrow for direct use and a panel graft must therefore be fashioned (*Figure 3*)[9,10]. End-to-end anastomosis in our hands had a poor outcome, probably because it was performed when a panel graft should have been inserted, although others have had greater success[17].

The minimum time between injury and restoration of blood flow is critical for limb survival[11] and insertion of an arterial shunt will permit temporary restoration of limb perfusion. When there is a combined arterial and venous injury or bilateral injuries, a shunt will permit arterial perfusion while the vein or opposite limb is repaired. In this study the median elapsed time from injury to restoration of arterial blood flow was over 7 h. Fasciotomy should be readily performed and probably routinely performed in limbs with a combined injury or injury to the popliteal vein[5,9,16]. The importance of other perioperative techniques such as postoperative limb elevation, arteriovenous fistulae, stockings and long-term anticoagulation with warfarin remains unproved but they are all theoretically attractive[6]. Five of our patients received low dose heparin and one received dextran in the early postoperative period and this may help to decrease the incidence of postoperative thrombosis. Three patients had a good result and the remaining repairs failed for technical reasons (i.e. a small saphenous vein graft). Experimentally, low molecular weight dextran has been shown to be superior to heparin[23].

Lower limb deep vein injuries remain a surgical challenge[24] but their management is no longer controversial[9,17]. Vein repair with either vein patch or a panel graft should be attempted in all patients unless other life-saving procedures require priority.

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Ultrasonographic screening of the abdominal aorta among siblings of patients with abdominal aortic aneurysms

H. Bengtsson,
Ö. Norrgård*,
K. A. Ängquist*,
O. Ekberg†,
L. Öberg‡ and
D. Bergqvist

Departments of Surgery and
†Diagnostic Radiology, University
of Lund, Malmö General Hospital,
*Malmö and *Departments of*
Surgery and ‡Diagnostic
Radiology, University of Umeå,
Umeå, Sweden
Correspondence to:
Dr H. Bengtsson, Department of
Surgery, General Hospital,
S-214 01 Malmö, Sweden

To evaluate the prevalence of abdominal aortic dilatations among asymptomatic brothers and sisters of patients with abdominal aortic aneurysms (AAAs), an ultrasonographic screening study was performed. One hundred and two siblings of patients operated on for AAAs at two Swedish hospitals were invited to attend, and 87 of them (35 men and 52 women) from 32 different families, accepted the invitation. Their median age was 63 years (range 39–82 years). Aortic dilatation was diagnosed in ten of the brothers (29 per cent) and three of the sisters (6 per cent). In ten cases (eight men and two women) there was a localized dilatation caudal to the coeliac axis, and in three a general dilatation of the abdominal aorta with the diameter at the coeliac axis > 29 mm. None of the aortic dilatations had been known before this study was performed. The conclusion is that the prevalence of asymptomatic aortic dilatations among brothers of patients with AAAs seems to be high and that this group should be selected for further screening studies.

Keywords: Abdominal aortic aneurysms, ultrasonographic diagnosis

Abdominal aortic aneurysms (AAAs) are responsible for about 1·3 per cent of the deaths among men aged over 50 years both in the UK and in Sweden, and the proportion has been increasing[1,2]. The true mortality rate from ruptured AAAs is as high as 85–95 per cent when both the subjects operated on and those not operated on are included[3–5], while the rate at elective operations is < 5 per cent in many centres[6–8]. To reduce the total mortalities, it is necessary to increase the percentage diagnosed and operated on electively. However, many of the AAAs are more or less asymptomatic[2,9], and the only way to diagnose these aneurysms before rupture is by screening. Screening of the whole population is unrealistic because of the costs in money and other resources[10], but, if defined groups with a high prevalence could be found, screening of these groups might be more cost effective.

One group that may be a potential target for a screening programme are siblings of patients with AAAs. Clinically apparent AAAs are common in this group[11–14], but nothing is known about the prevalence of asymptomatic AAAs. The purpose of the present study was to investigate the prevalence of previously unknown aortic dilatations among siblings of patients operated on for AAAs.

Patients and methods

The study was based on brothers and sisters of 84 patients (66 men and 18 women) who had been operated on for AAAs at two Swedish hospitals during the years 1981–86, and who were still alive on 1 September 1987. Twenty-nine of the operations had been performed at the Department of Surgery, University Hospital of Umeå, in the northern part of Sweden, and 55 at the Department of Surgery, Malmö Allmänna Sjukhus, University of Lund, in the southern part of Sweden. Information about the patients was obtained from the hospital register. A questionnaire was sent to the 84 patients requesting the names and the addresses of all their brothers and sisters who were still alive. Eighty-one patients (96 per cent) answered the questionnaire, and 159 of their brothers and sisters (60 brothers and 99 sisters) were still alive. However, in 57 cases (15 brothers and 42 sisters) these siblings were living abroad or far away from the investigating centres, and they were excluded. The remaining 102 siblings (45 brothers and 57 sisters) were invited to attend, and 87 (35 brothers and 52 sisters) accepted the invitation (85 per cent).

The median age of the attenders was 63 years (range 39–82 years), with no sex difference. They were from 32 different families, 13 from the area of Umeå with 42 siblings, and 19 from the area of Malmö with 45 siblings. The number of examined siblings in each family was one in 12 cases, two in eight cases, three in three cases, four in four cases, five in one case, six in two cases, eight in one case and nine in one case.

The siblings attending the study were fasted for at least 4 h before the examination. The examination of the aorta was in all instances performed by ultrasonography, using real-time equipment. The abdominal aorta was examined throughout its length, and the external diameter perpendicular to its length axis was registered at the level of the coeliac axis, just cranial to the aortic bifurcation and, when there was a localized dilatation caudal to the coeliac axis, at the level where the diameter was maximal. Aortic dilatation was defined as a localized dilatation of the abdominal aorta caudal to the level of the coeliac axis and/or an abdominal aorta > 29 mm in maximal diameter at the level of the coeliac axis. The examinations, by radiologists experienced in ultrasound techniques, were performed in 25 cases in Umeå, in 46 cases in Malmö, and in 16 cases at seven hospitals surrounding Umeå.

The attenders were asked about smoking habits, previous myocardial infarctions, cerebrovascular lesions and operations, whether they were taking antihypertensive drugs, and whether they were suffering from diabetes mellitus. The subjects examined in Umeå or Malmö had a general physical examination, including body weight and height, auscultation of peripheral pulses, and registration of blood pressure in both arms and in the ankles. The χ^2 test was used to test differences in proportions between groups, with Yates' correction when samples were less than five, and the two-tailed Mann–Whitney U tests were used to ascertain differences between groups concerning ordinal observations. P values $< 0{\cdot}05$ were considered as statistically significant.

Results

Abdominal aortic dilatation was found in ten brothers and three sisters. The frequency among the brothers was 29 per cent (95 per cent confidence interval 14–44 per cent), and among the sisters 6 per cent (95 per cent confidence interval 0–12 per cent). Ten of the affected siblings, eight men and two women, had a localized dilatation of the abdominal aorta caudal to the coeliac axis, with maximal diameters of 28 (woman), 33, 35, 36 (woman), 36, 37, 37, 42, 56 and 65 mm. The diameters at the coeliac axis in the same patients and in the same order are 20,

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28, 26, 25, 24, 20, 23, 17, 24 and 26 mm. The other three affected siblings, two men and one woman, had a general dilatation of the abdominal aorta, with maximal diameters of 33 (woman), 33 and 34 mm at the level of the coeliac axis. The mean (s.d.) diameter of the aorta of those without aortic dilatation was 22·2 (3·2) mm at the level of the coeliac axis, and 17·0 (2·7) mm just cranial to the aortic bifurcation.

The median age of the affected brothers was 62 years (range 49–73 years), and the ages of the three affected sisters were 61, 71 and 74 years. The siblings with aortic dilatation did not differ in age from those without ($P = 0·99$). Eleven of the brothers in the study were less than 60 years of age, and in this group four had aortic dilatation. The youngest affected sibling was a 49-year-old brother with a localized dilatation of the abdominal aorta.

Three of the affected siblings (two men and one woman) were of the same family, in which six siblings were examined, while the other ten were from ten different families. Six subjects with aortic dilatation (five men and one woman) were found among the siblings from Umeå, and seven (five men and two women) among those from Malmö. All the diagnosed aortic dilatations were asymptomatic and had not been known before this study was performed.

Nine of the siblings with aortic dilatation (69 per cent), but only 16 of those without (22 per cent), were taking antihypertensive drugs. This difference is statistically significant ($P < 0·001$). Both systolic ($P = 0·02$) and diastolic ($P = 0·03$) blood pressure (with eventual antihypertensive drugs) was significantly higher among the 13 subjects with aortic dilatation than among 64 subjects without. The ankle:arm blood pressure index was below 1·0 in six out of 70 examined siblings, and two of these (one man and one woman) had aortic dilatation. Seven siblings, all of them men, had been treated for myocardial infarction. Five of the ten men with aortic dilatation, but only two of the 25 men without, had had myocardial infarction. This difference is statistically significant ($P = 0·01$). Two siblings, one man and one woman, suffered from diabetes mellitus, but they did not have aortic dilatation. Ten of the siblings with aortic dilatation (77 per cent), and 40 of those without (54 per cent) were smokers. This difference is not statistically significant ($P = 0·47$). The men with aortic dilatation were not statistically taller ($P = 0·73$) or heavier ($P = 0·081$) than those without.

Discussion

The purpose of the present study was to evaluate the prevalence of aortic dilatation among living brothers and sisters of patients operated on for AAAs, and therefore no effort was made to get information about clinically diagnosed and ruptured AAAs among the deceased brothers and sisters. However, one of the brothers, who was still alive, had been operated on for an AAA.

The study was retrospective in the sense that the siblings were not registered at the time of aortic surgery. Fifty-seven siblings were excluded for geographical reasons, but this did not influence the representiveness of the sample. Fifteen siblings refused examination, but both the proportion of men and the median age was higher in this group than among the attenders, and there is therefore no reason to suspect a lower prevalence of aortic dilatation in this group. As far as we know, none of the attenders had any symptoms making them more prone to attend than others.

Ultrasonography was used to examine the aorta; it is a well established method[15–17]. All the ultrasonographic examinations were performed by radiologists experienced in ultrasound techniques; therefore the prevalence of aortic dilatations was not caused by misinterpretation of the findings. The definition of aortic dilatation that was chosen is based on the diameter of the normal abdominal aorta which decreases from the level of the coeliac axis caudally[18]; the upper limit of normality of the diameter at the coeliac axis has been proposed to be 29 mm[18–19].

Little is known about the prevalence of aortic dilatation in the population, and only three ultrasonographic studies have been published. Scott and Ashton[20] found 2·7 per cent (95 per cent confidence interval 1·5–4·0 per cent) aortic dilatations, defined as an abdominal aortic diameter >35 mm, in a group of men and women aged 65–85 years[20]. If the same definition was used in the present study, 17 per cent of the brothers (95 per cent confidence interval 4·7–29·6 per cent) would have had aortic dilatation. Collin *et al.*[21] found 3·4 per cent aortic dilatation (95 per cent confidence interval 1·2–6·7 per cent), defined as a diameter exceeding 32 mm, in a group of men aged 65–79 years[21]. The latter study could be compared with our results because the aortic dilatation among men in our study had a diameter >32 mm. The prevalence among the men in our study was 29 per cent. Collin *et al.*[22] have recently published another screening study of 426 men aged 65–74 years. In their study AAA was defined as an infrarenal aortic diameter >39 mm or exceeding the suprarenal aortic diameter by at least 5 mm. They found 5·4 per cent with AAAs (95 per cent confidence interval 3·3–7·5 per cent). With the same definition in the present study 23 per cent of the brothers (95 per cent confidence interval 8·9–36·8 per cent) had AAAs.

The occurrence of clinically diagnosed and ruptured AAAs among the deceased and living blood relatives of patients with AAA has been investigated in at least four studies. In one of these the incidence among the brothers and sisters of the patients was 1·9 per cent[11], and in another one it was 7·3 per cent[14]. In a third study, where the family histories of AAA-patients and controls were compared, AAAs were 11·6 times more common among the first degree relatives (brothers, sisters, parents, children) of the patients[13]. These figures are not directly comparable with the figures in the present study, because we were investigating the prevalence of aortic dilatations among asymptomatic siblings, but they show that familial aggregation of AAAs exists. A multifactorial mode of inheritance has been proposed, with at least one gene on the X chromosome[11–14]. This has been supported by studies of genetic markers and serum levels of lipids which, to some extent, are genetically determined[23–27].

In the studies concerning clinically diagnosed AAAs in the family the most common pattern was that only one blood relative was affected apart from the proband, but instead a high proportion of the probands had affected siblings[11,13,14]. In the present study 11 out of 32 probands (34 per cent) had siblings with aortic dilatations, and in ten of these families only one brother or sister was affected. On the other hand only one or two siblings from each family were examined in most of the families in the present study. More extreme families have also been described. In a study based on reports from several centres in the USA, Tilson and Seashore[12] described families with up to six affected siblings, with affected siblings from three generations, and with affected identical twins. In one of the families in the present study three out of six examined siblings had aortic dilatation, apart from the proband.

Comparison with other ultrasonographic screening studies of risk groups concerning the prevalence of aortic dilatation indicates that the prevalence is higher among brothers of patients who have had aneurysm surgery than among patients with various atherosclerotic manifestations or hypertension[28–33].

The prevalence of AAAs increases with age[34,35]. In our study there was no difference in age between those with and those without aortic dilatation. The blood pressure was higher among those with aortic dilatation than among those without, and a history of drug-treated hypertension was also more common in the first group. This is in agreement with the results of other studies[30]. Myocardial infarction was more common among the men with aortic dilatation than among those without, and this is also in accordance with other studies[25,36].

In conclusion the prevalence of asymptomatic aortic dilatation among the brothers of AAA-patients seems to be high, and this group must be considered for further screening programmes. Before more firm recommendations can be made, it is necessary to evaluate the prognosis of the aneurysms and dilated aortas discovered in screening studies, and to evaluate the cost effectiveness of such screening.

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Acute ischaemia of the lower limb: the effect of centralizing vascular surgical services on morbidity and mortality

A. E. Clason,
P. A. Stonebridge,
A. J. Duncan,
B. Nolan,
A. McL. Jenkins and
C. V. Ruckley

Vascular Surgery Unit, The Royal Infirmary, Edinburgh EH3 9Y W, UK
Correspondence to:
Mr A. E. Clason

Surgical audit data for two 5-year periods (1974–78 and 1983–87) have been compared in a Health Board Area to assess the impact of centralization of emergency vascular services on the treatment of the acutely ischaemic lower limb. Patient populations in each period were comparable. Mortality rates remained constant in both periods at approximately 30 per cent. A significant improvement in overall limb salvage was observed (from 54 to 67 per cent, $P < 0{\cdot}05$*). Limb salvage in survivors was improved from 80 to 95 per cent (*$P < 0{\cdot}001$*) and was paralleled by an increase in the number of reconstructive vascular procedures performed. We concluded that the centralization of emergency vascular services has not led to a reduced risk of mortality but has been associated with improved limb salvage.*

Keywords: Acute lower limb ischaemia, morbidity, mortality, centralization

The recent Report of the Confidential Enquiry into Perioperative Deaths (CEPOD) has highlighted the provision of emergency care for vascular disease as a problem area and a cause for concern[1]. In the UK, vascular surgery is not yet recognized as a separate speciality. The majority of vascular procedures are performed by general surgeons with variable vascular training and many other demands on their time. Few areas offer a regionalized service staffed by surgeons who work exclusively in the field. Increasing vascular workloads are reported[2,3] and the greater longevity among the population makes it likely that this trend will continue. The management of the acutely ischaemic limb, although revolutionized by the advent of the balloon embolectomy catheter[4], remains problematical. The operation of thromboembolectomy is a relatively simple procedure, but is still followed by high amputation and mortality rates. A vascular surgical unit providing a supra-area vascular emergency service for the three Health Board areas of south-east Scotland was formed in Edinburgh in 1982. The purpose of this study was to assess the impact of centralization of vascular services on the outcome of the acutely ischaemic lower limb.

Patients and methods

Two separate 5-year periods were examined: the period 1974–78 when vascular services were provided largely by general surgeons, and the period 1983–87 after the establishment in 1982 of a regional vascular service manned by three consultant vascular surgeons and their junior staff. During the period 1978–82 there was an increasing trend in Edinburgh towards centralization of vascular services. Whilst the majority of vascular emergencies were handled by the unit destined subsequently to provide an integrated supraregional service, a substantial number of cases were managed by general surgeons with varied experience of vascular surgery. In contrast, from 1982 all vascular emergencies in south-east Scotland (population approximately $1{\cdot}2 \times 10^6$) were referred to the new unit at the Royal Infirmary of Edinburgh. The period 1974–78 was chosen because it was considered most representative of a time period before the centralized service was available.

Patients admitted with acute lower limb ischaemia were identified from unit statistics assembled annually for the Lothian Surgical Audit. For the first 5-year period the audit data were prospectively collected and hand processed by individual units. During the second 5-year period all operative procedures were prospectively recorded and identified by a computerized coding system[5]. Identified cases were checked against operation record books and individual case notes and the relevant data extracted. The Audit includes details of all deaths on surgical units whether or not the patients had an operation. No alteration in patient management occurred between the two study periods. Patients with occlusive events following trauma or after previous arterial reconstruction were not included.

Patients were either given heparin and underwent emergency thromboembolectomy using a standard balloon catheter technique, or were treated conservatively with heparin or streptokinase, unless the limb was clearly irrecoverable or the patient moribund on admission.

Results

Approximately 45 patients with an acutely ischaemic limb were referred for emergency treatment per annum, representing an incidence of 1:27 000 population. The patient characteristics in the study period (1983–87) and the reference group (1974–78) were similar (*Table 1*), with approximately 90 per cent coming to operation. In the earlier period 85 per cent of the operations were performed under local anaesthesia in contrast to 96 per cent in the later study period. Roughly similar distributions of emboli were encountered during both periods and more proximal lesions were associated with a higher mortality rate. Similar proportions of the study groups had cardiac arrhythmias or recent myocardial infarction as a likely source of embolism, and similar proportions of each group had evidence of pre-existing atherosclerotic arterial disease with a past history of intermittent claudication or absence of contralateral limb pulses on clinical examination.

Table 1 *Patient characteristics in the two periods under study*

	1974–78	1983–87
Total number	218	204
Average age	68	70
Age range	42–89	41–98
Male:female	0·62:1	0·94:1
Atrial fibrillation	(63)	(65)
Previous peripheral vascular disease	(60)	(67)
Operation rate	(90)	(88)
Level		
Aorta	34	31
Femoral	172	162
Distal	12	11

Figures in parentheses are percentages

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Table 2 *Vascular reconstructions during the two periods under study*

	1974–78	1983–87
Vein patch ± endarteriectomy	1	10
Femorofemoral crossover graft	2	4
Femoropopliteal bypass	1	4
Aortic bifurcation graft	0	2
Profundaplasty	0	2
Angioplasty	0	1
Total	4	23

Incidence of reconstructive procedures (Table 2)

Twenty-three patients in the second study period had additional vascular operative procedures performed in conjunction with embolectomy, of whom three died and a further two required a major limb amputation. Only four such procedures were undertaken in the earlier period and all were performed in patients admitted to general surgical units in which a surgeon with a vascular interest happened to be located.

Outcome (Table 3)

The mortality rates in both study periods were comparable at approximately 30 per cent although the range of mortality rates for individual units varied considerably (26–43 per cent) in the earlier period. However, overall limb salvage was significantly better in the later period (1983–87) than in the earlier period (1974–78): 67 *versus* 54 per cent, $\chi^2 = 5{\cdot}88$, $P < 0{\cdot}05$. Furthermore limb salvage in survivors showed an even more significant improvement (95 *versus* 80 per cent, $\chi^2 = 13{\cdot}8$, $P < 0{\cdot}001$) between the two periods and parallels the increase in the number of reconstructive procedures. It was also noted that the limb salvage rate for patients treated in a unit with a vascular interest improved from 57 to 67 per cent.

Discussion

The fact that the study periods were almost a decade apart is an obvious imperfection in the comparison. Nevertheless, there has been little change in the surgical management of acute lower limb ischaemia, embolectomy with a balloon catheter remaining the standard approach over the last 25 years. Improvements in patient care over the last decade, if significant, might be expected to have improved not only limb salvage rates, but also mortality. This did not occur. Previous studies[5,6] have indicated that the outcome of vascular operations depends principally on the judgement and experience of the individual surgeon and is not predictable purely on the basis of hospital size and workload. This appears to be confirmed by the appreciable improvement in morbidity and mortality rates after emergency aneurysm surgery in centralized vascular surgical units[7,8]. In the present study no corresponding improvement in mortality has been found in the management of acute lower limb ischaemia. The continuing high mortality rate confirms the recent experience of Galbraith *et al.*[9] where in a comparable population 42 per cent either died or required major limb amputation following thromboembolectomy. In the present study similar patient characteristics were found in both study periods, with the same proportion of high risk individuals, and so it may be inferred that mortality largely reflects concurrent disease in this aged population[10]. However, the morbidity (as measured by the overall limb salvage rate) shows a significant improvement. This must nevertheless be interpreted with a degree of caution for, whilst overall limb salvage rate improved from 54 to 67 per cent over the 9-year period, limb salvage in units with a vascular interest also improved from 57 to 67 per cent, perhaps partly attributable to increased exposure and earlier referral of such patients to the centralized service. As the vast majority of vascular emergencies in south-east Scotland are now handled by the new supraregional secondary referral service, analysis of its impact on the outcome of acute lower limb ischaemia can only be retrospective.

Table 3 *Outcome of the patients treated during the two time periods*

	1974–78	1983–87
Number of patients	218	204
Total limbs at risk	252	234
Conservative treatment	28	21
Non-operative deaths	11	9
Hospital death without gangrene	13 (6)	14 (7)
Hospital death with gangrene	58 (27)	48 (24)
Overall limb salvage	118 (54)	135 (67)
Units without vascular interest	66/127 (52)	—
Units with a vascular interest	52/91 (57)	—
Overall limb salvage in survivors	118/147 (80)	135/142 (95)
Units without vascular interest	66/86 (77)	—
Units with a vascular interest	52/61 (85)	—
Overall mortality	71 (32)	62 (30)

Figures in parentheses are percentages

Not all acutely ischaemic lower limb problems can be solved by balloon catheter thromboembolectomy alone, as a significant proportion may be secondary to pre-existing atherosclerosis and may require vascular reconstruction. The improvement in limb salvage rates may reflect the increased number of immediate vascular reconstructions performed in the later period (18 of the 23 patients who underwent a reconstructive procedure survived with both limbs intact). It is in this latter area that the advantage may lie of concentrating experience in a specialized service. With the generally accepted high cost of amputation and consequent care, it is possible that the extra expense of transportation incurred by the centralization of the treatment of acute lower limb ischaemia is more than balanced by the improvement in limb salvage.

If the 13 per cent improvement in limb salvage were generally applicable (with an incidence of 1 in 21 000) then it would suggest that approximately 300 amputations resulting from acute ischaemia could be avoided each year in the UK. However, this too may be an underestimate as the continuing loss of limb and high mortality rate in our unit suggest that we need to review critically our methods of treating acute lower limb ischaemia.

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Capsular penetration and perforation in pleomorphic adenoma of the parotid salivary gland

H. H. Lawson

*Department of Surgery,
University of the Witwatersrand,
Baragwanath Hospital,
Medical School, York Road,
Parktown 2193, Johannesburg,
South Africa*

Correspondence to:
Professor H. H. Lawson

Both penetration and perforation of the capsule were seen on the superficial aspect of pleomorphic adenomas. Only penetration was noted on the deep aspect, where the tumour was adjacent to the facial nerve. In terms of local recurrence this may explain why it appears to be safe to separate the deep aspect of the tumour from the facial nerve without a wide margin of normal parotid tissue.

Keywords: Pleomorphic adenoma, capsule, recurrence

It is well recognized that after the simple procedure of enucleation, there is a recurrence rate of pleomorphic adenoma that varies from 20 to 45 per cent in the reported cases[1–3]. After wide excision with preservation of the facial nerve, recurrence rates from 0 to 2·5 per cent are reported[4–6]. In a recent series of 130 wide excisions for pleomorphic adenoma, followed up for a maximum period of 20 years, there was a single recurrence only[7]. In their important contribution, Patey and Thackeray[8] clearly showed what they termed 'focal infiltration' of the capsule, and demonstrated how pseudopodia of the tumour could be left behind if the lesion was enucleated. It is generally accepted that this is the explanation for tumour recurrence and the justification for the standard procedure of wide excision with preservation of the facial nerve.

The procedure of wide excision seems to work well in terms of avoiding tumour recurrence, even in very large tumours when the deep surface of the tumour impinges against the facial nerve. In these cases the nerve may be adherent to the tumour, from which it can only be separated with considerable difficulty. Certainly there is no macroscopically normal tissue between the nerve and the tumour.

Other authors have made the same observations with regard to large tumours, but have offered no explanations[5,6]. Hancock[6] has been so influenced by this observation that he now advocates removal of the tumour with only a covering of normal parotid tissue, and his reported recurrence rate over a follow-up period of 4 years is 1·6 per cent.

If the phenomenon of focal infiltration, or pseudopodia formation, was the only explanation for recurrence, why is there not a high rate of recurrence from tumour left in the region of the facial nerve after the removal of these large tumours?

The object of the present study was to compare the histopathology of the capsule on the deep surface of the tumour, where it was adjacent to the facial nerve, with the histopathology of the capsule on the superficial surface of the tumour, where it lay adjacent to normal parotid tissue.

Patients and methods

Seven patients, all with large lesions, greater than 5 × 7 cm clinically, underwent superficial parotidectomy for histologically confirmed pleomorphic adenoma of the superficial lobe of the parotid gland. The specimens were bisected in the sagittal plane into a deep and superficial part (*Figure 1*, line A–B). The superficial part of the capsule was defined as that part of the capsule lying on the superficial surface of the tumour between the tumour and normal parotid tissue (*Figure 1*,1). The deep part of the capsule was defined as that part of the capsule adjacent to the facial nerve (*Figure 1*,2). Multiple sections, and where necessary serial sections, were prepared in the horizontal plane above and below the lines C–D and E–F in *Figure 1*. All material was divided immediately after resection in this way and was fixed in 10 per cent formol saline. Using routine histological techniques and stains, the specimens were examined by conventional light microscopy.

Results

The superficial part of the capsule (Figure 1,*1*)

Two types of capsular involvement were observed and were present in all seven specimens.

1. *Capsular penetration*: an example is illustrated in *Figure 2*. The tumour can be seen as a nodular protrusion into the capsule, but at no point was there any disruption of the actual capsule between the tumour and normal parotid tissue. This observation was confirmed by serial section examination of the capsule over the whole area of the nodule.

2. *Capsular perforation*: this is illustrated in *Figure 3*. The tumour has clearly perforated through the whole thickness of the capsule, and can be seen lying adjacent to the normal parotid tissue.

Capsular penetration, which must obviously precede capsular perforation, was seen more frequently than perforation, and in many sections only penetration occurred. Where both features were seen in a single slide, with a capsule length of 300–400 mm, it was usual to see about five examples of penetration, and two or three examples of complete perforation. Capsular involvement did not occur in all sections, and could be missed if only limited material were examined.

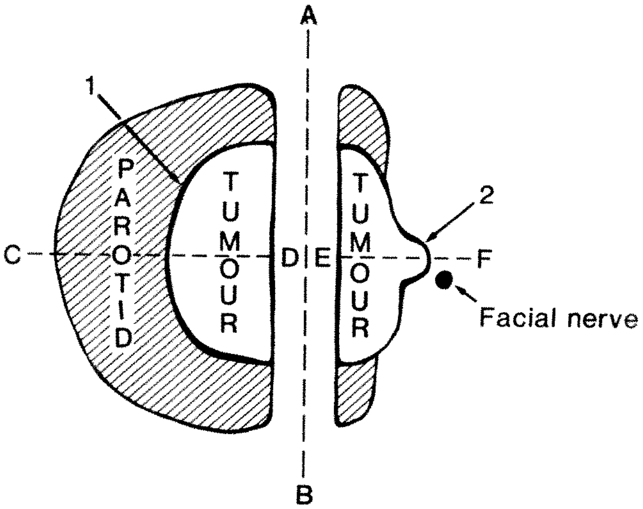

Figure 1 *Preparation of the specimen. Each specimen was divided along the line A–B initially. Multiple sections were prepared for histology above and below lines C–D and E–F. 1, Capsule between tumour and normal parotid tissue; 2, capsule adjacent to facial nerve*

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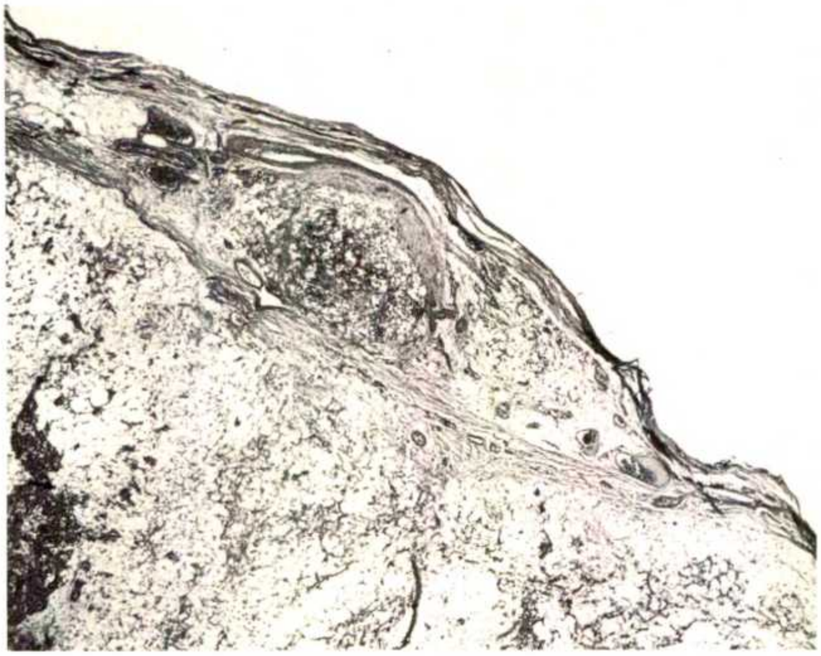

Figure 2 *Capsular penetration: the capsule superficial to the lesion is intact* (×25)

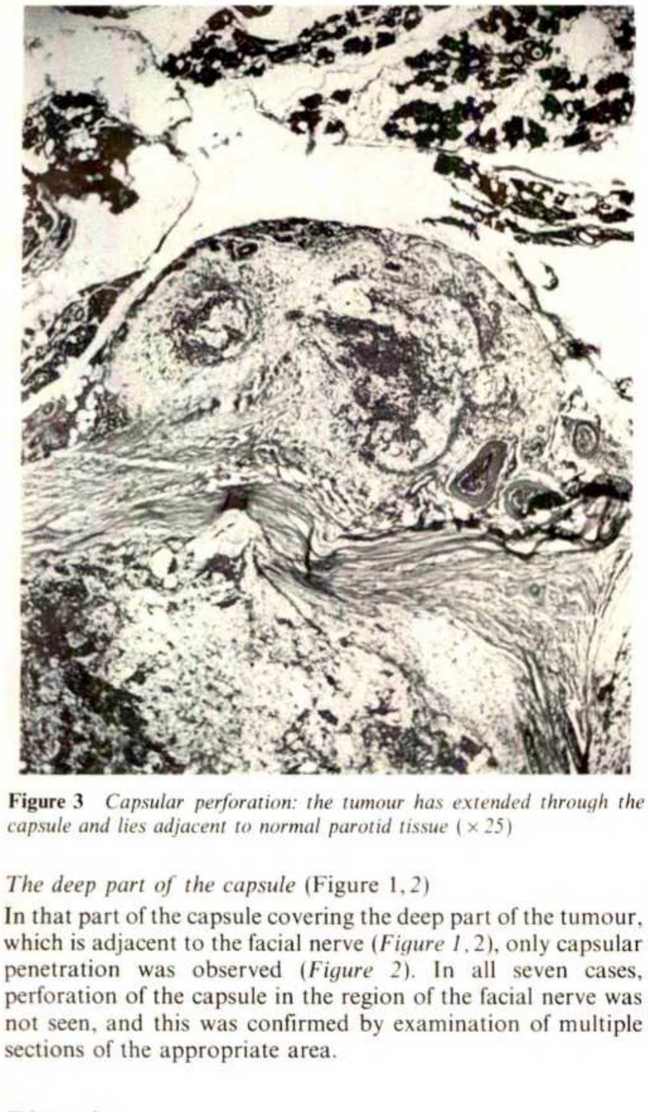

Figure 3 *Capsular perforation: the tumour has extended through the capsule and lies adjacent to normal parotid tissue* (×25)

The deep part of the capsule (Figure 1, *2*)

In that part of the capsule covering the deep part of the tumour, which is adjacent to the facial nerve (*Figure 1, 2*), only capsular penetration was observed (*Figure 2*). In all seven cases, perforation of the capsule in the region of the facial nerve was not seen, and this was confirmed by examination of multiple sections of the appropriate area.

Discussion

A description of the histopathology of pleomorphic adenoma would not be relevant in the present paper. An authoritative description has been given elsewhere[9]. Where the capsule is perforated by tumour (*Figure 3*) it is very likely that enucleation in the plane between its capsule and normal parotid tissue would result in incomplete removal of the tumour. Removal of the whole lesion could only be achieved if sufficient normal parotid tissue were removed at the same time. Where only capsular penetration is present (*Figure 2*), it is likely that enucleation in the same plane, i.e. between the tumour capsule and normal parotid tissue, would be successful in removing all the lesion.

In the present study, the only type of capsular involvement seen on the deep surface of the tumour was capsular penetration. Provided there was no breach of the capsule, this would offer an explanation for the observation that in the standard procedure of wide excision in large tumours, recurrence does not seem to occur as a result of tumour being left behind in relation to the facial nerve.

Where penetration of the capsule by the tumour has occurred, it has been pointed out that the phenomenon of subcapsular splitting, i.e. a split in the tumour lying within the capsule, may occur, while the capsule itself remains intact. If the surgeon entered this area inadvertently, this could be another reason for incomplete removal[8].

It is most unlikely that capsular perforation never occurs on the deep surface of the tumour in relation to the facial nerve, although it was not seen in the present study, which was limited to seven specimens. However, it does seem that it is at least an uncommon occurrence. The explanation for the observation is completely speculative. It is possible that capsular perforation is inhibited because of the very small restricted anatomical area of the parotid bed, bounded, as it is, anteriorly by the bone of the ramus of the mandible, posteriorly by the mastoid process, and above by the petrous temporal bone. The styloid process with its muscle and ligaments may provide a medially situated mechanical barrier.

The lack of any type of mechanical restraint in small peripheral tumours may allow capsular perforation to occur circumferentially around the whole tumour, which may explain the frequently quoted observation that recurrence seems to occur more often when small tumours are removed[3]. The same author writing in 1936 advised that the surgeon should wait until the 'tumour (is) ripe, that is about the size of a lemon'[3]. An increased frequency of focal infiltration of the capsule in small tumours has been recorded by others[8]. Even in large tumours, as in the present study, perforation of the superficial part of the capsule occurs; this was the case in all of the seven specimens examined here. The correct surgical procedure for the management of small or large pleomorphic adenomas of the parotid would therefore seem to be the standard operation of wide excision of the tumour with preservation of the facial nerve. The excellent results reported by Hancock[6], where less parotid tissue was removed, should be noted, although the follow-up period in that series is still relatively short.

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Short notes

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Cost effectiveness of ultrasound in primary parathyroid surgery

M. I. Kairaluoma, H. Mäkäräinen*, E. Salo-Zetterman, M. V. Kairaluoma and M. Ståhlberg

*Departments of Surgery and *Radiology, University of Oulu, SF-90220 Oulu, Finland*

Correspondence to: Dr M. I. Kairaluoma

It has been suggested that preoperative localization of enlarged parathyroid glands by ultrasound would facilitate neck exploration for primary hyperparathyroidism[1–5]. This study was undertaken to assess whether preoperative ultrasound is cost effective.

Patients and methods

The series consisted of 40 consecutive patients who underwent neck exploration for biochemically proved primary hyperparathyroidism at Oulu University Central Hospital. The first 20 patients operated on in 1978–81 did not undergo preoperative ultrasound examination, whereas the subsequent 20 treated in 1982–5 were subjected prospectively to preoperative ultrasound for localization of the enlarged parathyroid glands. The mean (s.d.) preoperative serum calcium concentration was 3·15 (0·22) mmol/l in the former group and 3·23 (0·24) mmol/l in the latter.

All the scans were performed by the same radiologist (H.M.)[6]. The scans were evaluated and reported before surgical exploration. All patients underwent neck exploration by the same surgeon (M.I.K.) in an attempt to visualize at least four parathyroid glands. Frozen section preparations from removed or biopsied parathyroid glands were examined at the time of operation during both series. The choice of operation was the decision of the surgeon. The operative findings were then compared with the preoperative ultrasound assessment by one of the team (E.S.-Z.) using the decision matrix described by McNeil and Adelstein[7]. All the patients were followed up until 31 December 1987.

Results

A solitary cervical adenoma was found in 16 and hyperplasia in four of the 20 patients in each group. In 18 of the 20 patients (90 per cent), the enlarged parathyroid gland was accurately located in tems of site and side whereas, in three studies, ultrasound incorrectly predicted the presence of an enlarged gland where none was found at operation (*Table 1*).

None of the patients died. Transient postoperative hypocalcaemia was encountered in four patients in both groups. In one patient operated on without preoperative ultrasound, the hypocalcaemia proved to be permanent. One other patient in the same group had transient one-sided vocal cord palsy. Two instances of persistent hypercalcaemia and one of recurrent hypercalcaemia occurred in patients without preoperative ultrasound. In the patients undergoing preoperative ultrasound, hypercalcaemia continued after operation in one case. Localization of the enlarged parathyroid glands by ultrasound before neck exploration significantly reduced the number of glands removed at operation and cut down the mean operative time by 20 min ($P < 0{\cdot}05$; *Table 2*). The operative time for the 17 patients with a true positive scan averaged 60 min and that for the remaining three patients with a false positive scan averaged 100 min ($P < 0{\cdot}01$).

Our operating room expenses for neck exploration are at present approximately £7 sterling per min and the total costs of ultrasound of the neck are £70. The total cost of preoperative ultrasound and subsequent neck exploration in patients with a true positive and false positive scan was £490 and £770, respectively. Therefore the overall cost for patients with preoperative ultrasound averaged £532 and that for patients without preoperative ultrasound before exploration £616. Preoperative ultrasound saved £86 per patient and an accurate ultrasound localization saved £126 in operation costs. The net saving arising from the use of preoperative ultrasound in the 20 patients was approximately £1700.

Table 1 *Nosological probabilities*

Nosological probabilities	No. of glands	Percentage
Sensitivity	18/20	90
Specificity	57/60	95
Accuracy	75/80	94

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Table 2 *Comparison of the results*

	No. of glands identified at operation	No. of glands removed at operation	Operative time (min)	Lowest postoperative serum calcium (mmol/l)
Without preoperative ultrasound	3·5 (0·9)	1·8 (0·8)	88 (34)	2·18 (0·21)
With preoperative ultrasound	3·7 (0·7)	1·2 (0·7)	66 (23)	2·17 (0·13)
P	n.s.	<0·001*	<0·05†	n.s.†

Figures are means with standard deviation in parentheses; n.s., not significant, $^*\chi_2$ test; †Student's *t* test

Discussion

The possible advantage of preoperative localization of the abnormal parathyroid glands is generally considered marginal[8]. Operative exploration of the neck nevertheless carries with it a risk of recurrent laryngeal nerve injury and hypoparathyroidism. In instances of adenoma, accurate preoperative localization may help to direct and limit the extent of dissection, and thereby reduce these associated risks. The degree of transient postoperative hypocalcaemia is related to the number of glands removed and biopsied[9]. Unilateral parathyroidectomy with preoperative ultrasound localization of an adenoma may reduce the risk of these complications[3,10]. In the present study there was no demonstrable difference in complication rates between the groups.

Ultrasound localization of the enlarged parathyroid glands before the initial neck exploration significantly reduced the number of glands removed, because the side and site of the glands to be removed was known to the surgeon. This was reflected in the operative time, which was 20 min shorter in this group. On the other hand, the results of a study using two consecutive groups is likely to be subject to errors derived from improved operative technique with increasing experience. It is concluded that the cost-effectiveness of preoperative ultrasound has not been proved, although ultrasound may facilitate and possibly shorten the operation in the future[1–2]. If surgery is limited to the removal of one enlarged gland and one ipsilateral normal gland, as suggested[3,5], accurate preoperative localization by ultrasound would perhaps allow unilateral neck exploration and thus reduce the operative time. In the case of multiglandular disease, a unilateral approach could, however, easily lead to missing double adenomas or asymmetrical hyperplasia on the opposite side.

We conclude that ultrasound reduces significantly both the number of glands removed and the mean operative time. The results suggest that ultrasound localization of the enlarged parathyroid gland before initial neck exploration for primary hyperparathyroidism may be cost effective.

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Phenol cauterization for ingrowing toenails: a review of five years' experience

D. S. Byrne and D. Caldwell*

*Departments of Surgery and *Chiropody, Stobhill General Hospital, Glasgow, UK*

Correspondence to: Mr D. S. Byrne, Department of Surgery, Gartnavel General Hospital, 1053 Great Western Road, Glasgow G12, UK

Ingrowing toenails are a common problem causing significant morbidity. Treatments used in the past have met with high failure rates, for example: simple avulsion, 64–70 per cent[1,2]; Zadik's procedure, 16–28 per cent[1,2]; surgical wedge resection of the nailbed, 25 per cent[1,3]; gutter treatment, 48 per cent[4]. In recent years phenol cauterization of the nailbed has been used increasingly. Our early experience of this technique showed a recurrence rate of only 3 per cent[5] and we have now completed a retrospective study of all the patients treated in this way at our clinic in the five subsequent years.

Patients and methods

Patients are referred to our clinic from the Accident and Emergency Department and surgical clinics of this hospital or directly by general practitioners, and are treated by a surgical senior house officers or a chiropodist. Our policy is to perform segmental ablation whenever possible, using a modification of Ross's technique[5,6]. 'Ring block' anaesthesia is used: the toe is exsanguinated by elevation and the application of a 2·5-cm width of an Esmarch bandage (Leyland Medical, Preston, UK); and a rubber tourniquet is placed around the base of the toe. A wedge of nail one-quarter of the total width is then resected from the affected edge using Thwaites' nail-nippers (Footman and Company Ltd., Mitcham, UK). After protecting the surrounding skin with petroleum jelly, 88 per cent phenol is applied to the exposed area, particularly to the sulcus and under the eponychium, using a Black's file (Footman and Company Ltd.) and cotton buds. After 3 min, this is neutralized with surgical spirit before applying a tulle gras dressing and releasing the tourniquet. Patients attend their practice nurse 24–48 h later for a change of dressing and return to the clinic 1 week, 1 month and 6 months postoperatively. They are then discharged if satisfactory healing has occurred.

Between January 1982 and December 1986, 1135 phenol ablations were performed on 850 patients attending this clinic. Reply-paid questionnaires were sent to 313 patients who defaulted from follow-up, enquiring about nail regrowth and recurrent symptoms. Of 162 who replied, 50 reported symptoms and were sent return appointments. The non-responders (151) were excluded from the study.

The 699 patients studied underwent 623 segmental ablations and 308 total ablations, 41 nails were treated on both edges, and 175 patients underwent simultaneous bilateral treatment. Nail spurs growing after previous surgical treatment were avulsed in nine cases and the residual nailbed cauterized. The sex ratio was 367 (male):332 (female) and the age range was 5–88 years (mean 24·9 years). Mean follow-up was 13 months (range 6–60 months).

Results

Sixty-five procedures (6·9 per cent) were deemed failures because of nail regrowth or recurrence of symptoms at the same site. Twenty-eight (43 per cent) of these were in patients who had defaulted from the clinic before 6 months. Twenty-four patients underwent second operations, and no failures were recorded after a minimum follow-up of 7 months (*Table 1*).

The recurrence rate after segmental ablation (4·5 per cent, $n=28$) was significantly better than that after total ablation (11·4 per cent, $n=35$; $P<0{\cdot}05$, testing for the difference between two proportions). All the failed total ablations showed regrowth of nail, which must result from inadequate destruction of the matrix owing to faulty technique or the phenol solution used. Nail regrowth was only apparent in 16 of the failed segmental ablations. The remainder, we believe, were due to insufficient width of nail being excised, resulting in recurrence of symptoms. This is supported by the observation that when both edges of the nail were treated and the width of nail consequently substantially reduced, failures (6 per cent, $n=5$) were all due to nail regrowth. The failure rate following ablation of both edges of a single nail (three of 41 toes, 7 per cent) compared favourably with that after total ablation (11·4 per cent) but this difference did not achieve statistical significance. Two patients undergoing removal of nail spurs had nail regrowth, and both were retreated successfully. Twelve patients had mistaken hyperkeratosis for nail regrowth after total ablations and were educated in the prevention of this condition.

Discussion

Although the first line of treatment of ingrowing toenails remains conservative, surgery is indicated for patients with persisting problems. Our study confirms the very low recurrence rate after phenol ablation observed by Ramsay and Caldwell[5] and reported in other smaller series[7–10]. The results following segmental ablation are particularly good but could be further improved by attention to some points of technique:

1. A sufficient width of nail must be removed. We recommend a full quarter
2. Care must be taken not to leave nail spicules in the sulcus or under the eponychium
3. The phenol must be applied particularly to the nailbed in these two sites and for sufficient time. Previous studies[7] have shown increased failure rates after application of phenol for less than 3 min
4. Absolute haemostasis is essential as blood partly neutralizes the cauterizing effect of phenol[11].

Total ablation of the nailbed has been recommended as the treatment of choice for all ingrowing toenails[7] and specifically for nails affected on both edges[8]. Our results show that segmental ablation produces significantly better results than total ablation, and, although no significant difference between the results after treating both edges of one nail and after total ablation was observed, the preservation of at least part of the nail with the avoidance of hyperkeratosis are significant advantages to the patient. We recommend segmental ablation whenever possible.

Repeated failure has frequently been noted after surgical treatment of ingrowing toenails (e.g. 43 per cent after three avulsions, 34·5 per cent after a second Zadik's procedure[1]), and authors have even suggested that very aggressive techniques such as Syme's terminal amputation be employed after initial failure to avoid such high recurrence rates[12]. We observed no recurrences among the few patients who required a second operation (*Table 1*), and therefore these treatments are considered inappropriate and outdated.

Table 1 *Distribution and results of the ablative procedures used*

	First procedure		Second procedure	
Operation	*n*	Failures	*n*	Failures
Segmental ablation	623	28 (4·5)	7	0
Total ablation	308	35 (11·4)	11	0
Removal of spurs	9	2 (22)	6*	0

Figures in parentheses are percentages. * Four patients who had initially undergone total ablation of the nailbed subsequently underwent removal of regrowing nail spurs

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Of the documented failures in this study, 79 per cent occurred within 6 months of operation and this, together with previous observations that almost all failures occur within this period[12], support our postoperative review policy. This study confirms that segmental phenol ablation for ingrowing toenails produces excellent results and it is recommended as the treatment of choice for this condition.

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Clinical results of colectomy for severe constipation

K. Yoshioka and
M. R. B. Keighley

Department of Surgery, The General Hospital, Birmingham, UK
Correspondence to:
Professor M R. B. Keighley,
Department of Surgery, 4th Floor
West, Queen Elizabeth Hospital,
Edgbaston, Birmingham B15 2PH,
UK

Subtotal colectomy has been performed in 40 patients with severe constipation. Only one patient was male. Five patients (13 per cent) had a history of a serious psychiatric disorder. Twenty-six patients (65 per cent) could not expel a 100-ml air-filled balloon and 19 patients (48 per cent) had electromyographic evidence of abnormal puborectalis contraction during attempted defaecation before operation. Median preoperative passage of 50 radio-opaque markers over 5 days was 16 per cent. Sixteen patients had had a previous anorectal myectomy to exclude Hirschsprung's disease. Initial resections were subtotal colectomy and ileorectal anastomosis ($n = 34$)*, caecorectal* ($n = 5$) *or ileosigmoid* ($n = 1$) *anastomosis. Secondary operations included restorative proctocolectomy and ileal pouch–anal anastomosis* ($n = 6$) *and six patients eventually had an ileostomy. Median bowel frequency per week significantly increased after operation (0·3 (range 0–1) preoperatively to 21 (range 2–70) postoperatively,* $P < 0{\cdot}005$*), the percentage of patients with abdominal pain fell after operation from 93 to 39 per cent but symptoms of abdominal distension remained the same (86 per cent preoperatively and 82 per cent postoperatively).*

Keywords: Colectomy, constipation, anorectal myectomy, bowel frequency

In the early part of this century, Sir William Arbuthnot Lane (1909) advocated subtotal colectomy and ileorectal anastomosis for the treatment of a variety of disorders, including a condition referred to as chronic intestinal stasis[1]. The operation then fell into disrepute. Colectomy carries a morbidity risk and functional results may be disappointing, hence surgeons are understandably reluctant to remove a colon with no demonstrable structural abnormality[2]. More recently both colectomy with caecorectal anastomosis and colectomy with ileorectal anastomosis have been shown to achieve good results in slow transit constipation[3–6]. There is, however, an incidence of psychiatric disturbance in these patients and although subtotal colectomy often controls the constipation, abdominal pain and distension may persist.

We reviewed the clinical results of subtotal colectomy for severe constipation performed over the last 10 years.

Patients and methods

Colectomy has been performed in 40 patients with severe constipation between 1977 and 1987 One patient was a man and 39 were women. The median age was 35 years (range 19–72 years).

Anal manometry, assessment of rectal sensation and electromyography of the puborectalis were performed in all patients before operation. Colonic transit was studied in all except three patients but colonic motility was evaluated in only 16. The median clinical follow-up was 3 years (range from 5 months to 10 years). A questionnaire was sent to some patients who no longer lived locally to obtain a complete follow-up.

Physiological studies

Anal canal pressures were measured in the left lateral position after rectal examination using a closed water-filled balloon probe attached to a transducer and pen recorder as previously described[7,8] Measurement of resting and squeeze anal pressures were performed at 1-cm intervals 1–5 cm from the anal verge The maximum squeeze pressure was the highest pressure recorded after repeated voluntary contractions at each recording site With a soft latex balloon positioned in the rectal ampulla just above the levator ani, the response of the resting anal pressure to distension with incremental 50-ml aliquots of air to a volume of 400 ml was monitored. A reduction of more than 10 per cent of the resting pressure was recorded as an intact rectoanal inhibitory reflex.

Rectal sensation was assessed using the same rectal balloon. Three parameters of sensation were recorded according to the criteria of Farthing and Lennard-Jones[9] threshold volume, volume associated with constant rectal sensation and volume below 400 ml at which pain became intolerable (maximum tolerable volume). In many of the constipated patients 400 ml caused no apparent discomfort, but a further increase in volume was not attempted for fear of bursting the balloon

The patients were asked to expel a balloon filled with 100 ml of air to evaluate rectal evacuation. During the last 4 years all patients ($n = 27$) have been evaluated by videoproctography in which 100 ml (120 g) of a suspension of Barritop® (Concept Pharmaceuticals, UK) and cellulose is introduced into the rectal ampulla and the anal canal marked with radio-opaque paste. The perineal skin and symphysis pubis are marked using a harness to assess degrees of perineal pelvic floor descent. The anorectal angles are measured at rest, during pelvic floor contraction and during defaecation from frozen frames using a lateral X-ray screening technique that allows measurement of the long axes of the anus and rectum, the latter being determined by calculation of the centroid from a computer program. The degree of rectal evacuation is measured by collection (weight) of contrast material passed in 1 min Any morphological abnormality such as gross perineal descent or rectal intussusception was noted and such patients were excluded from treatment by subtotal colectomy.

Electromyography of the pelvic floor was recorded using a concentric needle electrode at rest and during pelvic floor contraction and attempted defaecation.

Colonic transit was assessed while the patient was eating a normal diet and taking no laxatives. Fifty radio-opaque pellets were taken by mouth and a plain X-ray of the abdomen was obtained 5 days later. Transit was recorded as the percentage of radio-opaque markers passed in 5 days

Sigmoid motility was assessed in 16 patients using a double-lumen catheter placed with its openings at 15 and 20 cm from the anal verge during sigmoidoscopy. The catheter was taped into position and the recording tubes were perfused with saline using an infusion pump at a rate of 2 ml/min Pressures were recorded at both sites at rest for 30 min, followed by a further 30 min after colonic stimulation using 5 mg intrarectal bisacodyl

Operative procedures

All patients underwent subtotal colectomy, 34 had an ileorectal anastomosis, five had a caecorectal and one had an ileosigmoid anastomosis.

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Earlier surgical procedures

If there was any evidence of rectal dilatation on barium enema, if the rectoanal inhibitory reflex was absent or if there was impaired rectal emptying, patients underwent an anorectal myectomy as already described, both as a potential therapeutic measure and to exclude short segment Hirschsprung's disease[10]. For these reasons 16 patients underwent a preliminary anorectal myectomy; none experienced any long-term benefit from this operation and, because of objective evidence of colonic stasis, the patients later underwent subtotal colectomy. If the rectoanal inhibitory reflex was absent but rectal evacuation was normal, patients had a series of full-thickness rectal biopsies to exclude Hirschsprung's disease; this practice was undertaken in seven of these patients. Before our practice of using anorectal myectomy for outlet obstruction, partial pelvic floor division was used; one such patient in this series had this operation before subtotal colectomy.

Selection of patients

During the period of observation 131 patients underwent some form of operative intervention for chronic long-standing constipation (*Table 1*). Anorectal myectomy was used in 84 patients, although ten of these patients had had an earlier biopsy to exclude Hirschsprung's disease Rectal biopsies had been used in 26 patients, partial puborectalis division in six, rectopexy for secondary rectal prolapse in patients with underlying constipation in 20 and partial subtotal colectomy as a primary procedure in only 15 patients.

Subtotal colectomy was used in 22 patients with slow transit constipation and rectal inertia and in 18 patients having colonic inertia alone. We preferred to offer subtotal colectomy only to those individuals in whom rectal evacuation was normal but there were many patients who continued to require repeated enemas or large doses of laxatives in the group with anismus and colonic stasis in whom colectomy was eventually undertaken.

Results

All patients were shown to have idiopathic slow transit constipation according to the results of our physiological assessment. In addition, megacolon or megarectum was demonstrated on barium enema examination in eight patients, two patients had histological evidence of Hirschsprung's disease and one patient developed severe constipation after rectopexy for full-thickness rectal prolapse. The median history of constipation in the 40 patients having subtotal colectomy was 20 years (range 1–60 years).

Five patients had been previously admitted for psychiatric disorders; three had a history of anorexia nervosa and two had had severe depression.

Twelve patients (30 per cent) have now required further operations after colectomy (*Table 2*). Six patients have had an ileostomy; two of these patients have also undergone a rectal excision. One of these patients had Hirschsprung's disease and could not defaecate even after ileorectal anastomosis and required an ileostomy. She eventually requested a proctectomy and a permanent stoma. The other patient had persistent defaecatory problems and rectal pain after subtotal colectomy and ileorectal anastomosis and eventually requested an end ileostomy and rectal excision. One patient whom we suspect is a chronic abuser of laxatives had such severe diarrhoea after ileorectal anastomosis that she requested an ileostomy. The other three patients were unable to defaecate despite patent ileorectal anastomosis; there was no evidence of megarectum, but none could evacuate material from the rectal ampulla on videoproctography and they all have now elected to have a loop ileostomy.

Six patients have developed a megarectum and impaired rectal sensation with recurrent severe constipation after subtotal colectomy and ileorectal anastomosis and three of the patients were also shown to have rectal inertia on videoproctography. All of these patients have had a restorative proctocolectomy and ileal pouch–anal anastomosis. Three have a duplicated J pouch while the remaining three have a four-lumen W pouch All six patients with pouch–anal anastomosis have complete control of defaecation, and bowel frequency ranges from two to eight times in 24 h but three still complain of abdominal distension and pain. Two of the six patients with pouches originally had a caecorectal anastomosis; the caecum became dilated and they underwent caecal excision and ileorectal anastomosis before further constipation supervened from megarectum.

Results of the preoperative physiological studies are shown in *Table 3*. Anal sensation did not differ from that in a previous group of age- and sex-matched controls Rectal sensation was normal in all except the eight patients with a megarectum. The rectoanal inhibitory reflex was absent in 14 patients (35 per cent), two of whom were shown to have Hirschsprung's disease. Twenty-six patients (65 per cent) were unable to pass a balloon containing 100 ml of air and 19 (48 per cent) exhibited electromyographic evidence of increased electrical activity of the

Table 1 *Initial operation*

		Preoperative symptoms			
No. of patients	Initial operation	Rectal inertia alone	Rectal inertia and slow transit	Slow transit alone	Subtotal colectomy
84	Anorectal myectomy ($n = 74$ alone)	54			0
			28		14
				2	2
26	Rectal biopsies to exclude aganglionosis ($n = 16$ alone)	16			0
			10		7
				0	0
6	Partial puborectalis division ($n = 6$ alone)	3			0
			3		1
				0	0
20	Rectopexy for intussusception or prolapse ($n = 20$ alone)	0			0
			7		0
				13	1
15	Subtotal colectomy ($n = 15$ alone)	0			0
			0		0
				15	15
	Total having colectomy	0	22	18	40

Table 2 *Further operation after colectomy*

Restorative proctectomy and ileal pouch–anal anastomosis	6
Ileostomy alone	4
Ileostomy and later rectal excision (after anorectal myectomy)	1
Pelvic floor division + ileostomy + rectal excision (after anorectal myectomy)	1
Total	12

Table 3 *Physiological studies before operation*

Maximum anal pressure (cmH_2O)	100 (60–150)*
Maximum squeeze pressure (cmH_2O)	210 (80–340)*
Rectal sensation (ml).	
Threshold	50 (50–150)*
Constant sensation	150 (100–400)*
Maximum tolerable volume	400 (250–400)*
Absent rectoanal inhibitory reflex	14 (35%)
Inability to pass a balloon containing 100 ml air	26 (65%)
Percentage rectal emptying on videoproctography ($n = 27$)	63 (0–94)*
Increased electromyography of the puborectalis during attempted defaecation	19 (48%)
Colonic transit (percentage of markers passed in 5 days)	16 (0–96)*
Colonic motility no response to bisacodyl ($n = 16$)	9 (56%)

*Median and range

puborectalis muscle during attempted defaecation. Seventeen of the 27 patients having videoproctography passed less than 10 per cent of the rectal instillate in 1 min (63 per cent). Colonic transit studies showed that only six patients (15 per cent) passed more than 60 per cent of markers in 5 days and it was thought that all of the patients had taken laxatives after swallowing the pellets. Colonic motility was studied in 16 patients and in nine (56 per cent) there was no response to the administration of bisacodyl. Overall 55 per cent of patients were found to have both outlet obstruction and an inert colon.

Bowel frequency was compared before and after subtotal colectomy in 28 patients (*Figure 1*). Preoperative median bowel frequency was 0·3 times per week (range 0–1 times per week) whereas it was 21 times per week (range 2–70 times per week) after operation ($P < 0.005$). Twelve patients were not assessed because they had had an additional operation. The incidence of abdominal distension and pain was compared before and after operation in those patients with a functioning ileorectal or caecorectal anastomosis (*Table 4*). Twenty-six of these patients (93 per cent) complained of abdominal pain before operation but this persisted in only 11 patients (39 per cent) after operation ($P < 0.02$). Improvement in pain was significantly more common in patients who had had an anorectal myectomy before colectomy because of associated rectal inertia than in those who had not ($P < 0.05$). Abdominal distension was a feature in almost all patients before colectomy and almost invariably persisted.

Twenty-six patients developed complications after operation. Severe diarrhoea was recorded in 13 patients, three of whom had severe perianal excoriation. One of these patients had so much trouble that an ileostomy was raised and one patient with some evidence of perineal descent became incontinent. Fortunately she improved after a later postanal repair. Four patients developed small bowel obstruction and one of these required laparotomy and eventually an ileostomy. Pelvic sepsis was observed in three patients and followed a contained leak from the anastomosis in two. Only one patient had to be returned to theatre to take down the anastomosis; intestinal continuity has now been restored Wound infection occurred in three patients, all of whom had also had pelvic sepsis. Troublesome and repeated small bowel obstruction was recorded in four patients, but only one required surgical intervention.

Some histological abnormality was observed in 22 patients. Melanosis coli was seen in five and an inflamed mucosa thought to be due to laxative abuse was seen in four. Special silver stains revealed some evidence of neuronal degeneration in all 13 colons examined in this way In three cases the appearances suggested a congenital abnormality and the remainder were thought to be acquired possibly from prolonged laxative use.

Discussion

Surgical management options for chronic constipation have ranged from intra-abdominal sympathectomy[11], through vary-

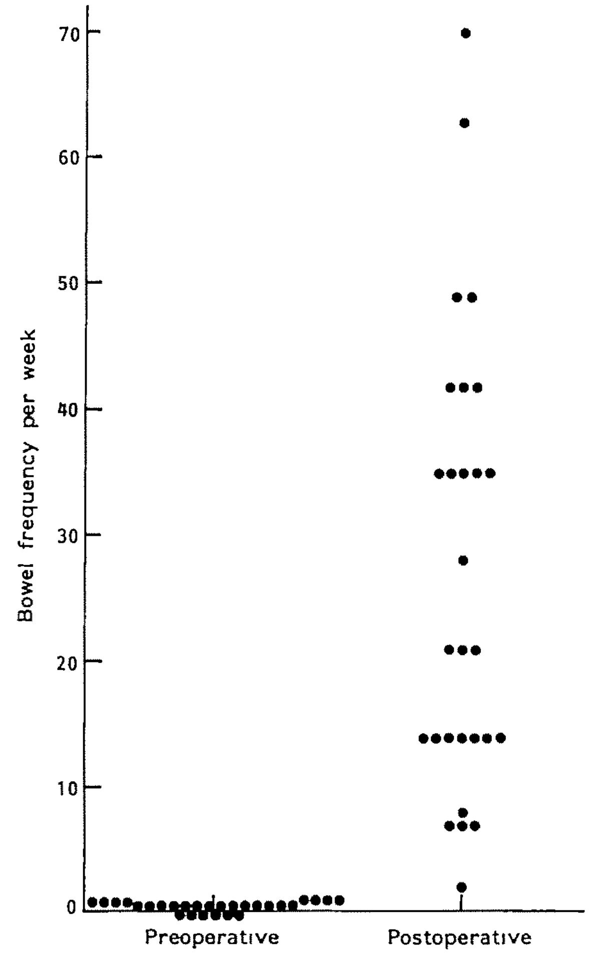

Figure 1 *Bowel frequency before and after operation,* $P < 0.005$ *preoperative* versus *postoperative*

Table 4 *Abdominal pain and distension before and after operation in those who still have a functioning ileorectal or caecorectal anastomosis*

	Before operation	After operation	P*
Abdominal pain ($n = 28$)	26 (93%)	11 (39%)	<0·02
Without previous anorectal myectomy ($n = 16$)	15	8	n s.
With previous anorectal myectomy ($n = 12$)	11	3	<0·05
Abdominal distension ($n = 28$)	24 (86%)	23 (82%)	n s
Without previous anorectal myectomy ($n = 16$)	14	13	n s
With previous anorectal myectomy ($n = 12$)	10	10	n s

*Calculated using χ^2 one sample test; n s , not significant ing degrees of partial colectomy[12], to anorectal myectomy, but none of these procedures had proved to be completely reliable for slow transit constipation. Although improvement of bowel frequency and avoidance of laxatives and enemas have been reported following subtotal colectomy[2,4], results are unpredictable and some patients develop diarrhoea Furthermore, abdominal pain and distension may persist. Even when the bowel has been divided at the pelvic brim, the rectum sometimes dilates, resulting in recurrent constipation[13] Caecorectal anastomosis is sometimes associated with dilation of the caecum and recurrent constipation[14]; on the other hand the ileocaecal valve is preserved which might prevent bacterial overgrowth in the small bowel and attacks of pseudo-obstruction. Despite this theoretical consideration, we have now performed 14 further subtotal colectomies for slow transit constipation, there being an equal number of caecorectal and ileorectal anastomoses. No difference in the early functional results has been observed, small bowel transit assessed by breath hydrogen was similar in both groups and the incidence of abdominal distension was the same.

In this series, subtotal colectomy and ileorectal anastomosis was carried out in 34 patients. Subtotal colectomy and caecorectal anastomosis was performed in only five patients but two of these presented within 2 years with persistent constipation due to caecal dilation, one of whom developed a caecal volvulus. Both required conversion to an ileorectal anastomosis but both later developed a megarectum and have eventually had a restorative proctocolectomy. In view of these observations we see no merit in preserving the ileocaecal valve or the caecum and now prefer an ileorectal anastomosis.

The incidence of complications was high in our series. Thirteen patients developed severe incapacitating diarrhoea necessitating an ileostomy in one. Hughes *et al* [15] reported that 41 per cent of patients having partial or total colectomy for constipation subsequently required operation for acute small bowel obstruction due to adhesions. We experienced only four cases of small bowel obstruction after operation and only one required laparotomy. However, this patient required an ileostomy as she could not defaecate despite a patent ileorectal anastomosis even when the small bowel obstruction had been attended to.

The six patients who eventually underwent restorative proctocolectomy and pouch–anal anastomosis are very interesting. They all had a megacolon initially but the diameter of the rectum was judged to be normal. Over a variable number of years the rectum enlarged and became inert. Before restorative proctocolectomy all had solid faeces in the rectal ampulla despite the subtotal colectomy and all had gross impairment of rectal sensation. A balloon inflated with 400 ml of air caused no discomfort and was not even felt by three patients. All have obtained considerable benefit following pouch–anal anastomosis, bowel frequency ranging from two to eight times a day. None experienced soiling or incontinence, none takes antidiarrhoeal agents but three still complain of abdominal distension. All of these patients have been studied after operation The median maximum tolerated volume of the pouch was 350 ml and varied from 250 to 400 ml but all have normal proximal small bowel motility, and reflex contraction of the pouch was observed after distension with 200–300 ml of air. Median percentage pouch emptying was 55 per cent (range 30–75 per cent) It appears therefore that a large entirely inert rectum lacking sensory awareness to distension has been converted to a smaller reservoir which is capable of contraction after threshold distension volume.

Since 1984 we have routinely performed anorectal myectomy on patients with impaired rectal emptying and an absent rectoanal inhibitory reflex in order to exclude Hirschsprung's disease in an attempt to treat outlet obstruction We found that 62 per cent of patients with constipation were improved by anorectal myectomy[10]. Patients with outlet obstruction alone have a much better response to anorectal myectomy than those with evidence of anismus and colonic stasis[16]. Sixteen patients previously treated by anorectal myectomy required colectomy because of persistent constipation; all were improved after the operation and none developed incontinence. In patients with evidence of outlet obstruction and colonic inertia the combination of anorectal myectomy and colectomy might be followed by superior results. Certainly patients having this combination had significantly less abdominal pain than those having subtotal colectomy alone and rectal evacuation was improved. On the other hand it is sometimes difficult to interpret evidence of marker stasis in the colon if constipation is principally due to impaired rectal evacuation.

Preoperative physiological studies showed that 65 per cent of patients could not pass a balloon containing 100 ml of air, 48 per cent had electromyographic evidence of increased electrical activity in the puborectalis during defaecation and 43 per cent had impaired rectal evacuation on videoproctography. Hence over half of these patients (22 of 40) had evidence of rectal inertia as well as colonic stasis. Although 84 per cent of patients had delayed transit of markers only nine of 16 patients (56 per cent) did not respond to bisacodyl infusion The marker test is unreliable if patients take laxatives after their ingestion and a few of our patients found that they could not discontinue laxatives for 7 days because it made them feel ill to do so. However, these physiological studies were unable to predict patients who developed postoperative diarrhoea, or persistent constipation, abdominal pain and distension

The clinical role of these physiological tests needs to be evaluated. We believe that there should be objective evidence of colonic stasis or impaired rectal emptying before embarking on surgical procedures that may be attended by long-term morbidity. Measurement of colonic transit with radio-opaque markers is a crude way of assessing colonic inertia; markers will certainly be retained in the rectum if there is outlet obstruction, hence only markers retained above the pelvic brim should be counted. It is essential that laxatives are withheld for 5 days before and during the period between ingestion and X-ray. Since some patients tend to exaggerate the degree of disturbance, objective proof of colonic stasis is important and may have to be repeated. We have discontinued the use of sigmoid manometry to assess colonic inertia since positioning of the catheters may be difficult and time consuming; furthermore, administration of bisacodyl is sometimes painful. Diagnosis of outlet obstruction is important since we believe that anorectal myectomy is the treatment of choice, videoproctography is now our preferred investigation and electromyography and balloon evacuation are probably unnecessary. As anorectal myectomy is the most reliable way of identifying Hirschsprung's disease and as histopathological evidence of aganglionosis does not correlate with an absent rectoanal inhibitory reflex, anal manometry seems largely superfluous We now believe that selection of patients for the operation can be reliably performed by repeated colonic transit marker studies and videoproctography.

As a result of this experience, we believe that surgical therapy for constipation should only be considered for psychologically stable patients with an identifiable physiological abnormality. If symptoms are intractable and there is evidence of colonic stasis we would now advise a subtotal colectomy and ileorectal anastomosis. If there is outlet obstruction with or without colonic inertia, anorectal myectomy would be advised both for diagnostic and therapeutic purposes. However, patients with both abnormalities must be warned that a subtotal colectomy may be needed if there is no response to anorectal myectomy alone.

Overall only 23 of 40 patients are satisfied with their operation and even then many complain of abdominal pain, bloating or diarrhoea. Twelve patients have required further surgical treatment. Six now have an ileostomy and the other six have required restorative proctocolectomy because of impaired rectal sensation and evacuation. There are few reports of restorative proctocolectomy for functional bowel disease, but the results in six patients who would otherwise have faced a permanent ileostomy are encouraging. We believe that secondary megarectum is an indication for this operation as all our patients are continent and are able to defaecate; however, three of six still complain of abdominal pain and distension.

It is disappointing that the physiological results are unable to predict those patients having a poor outcome. In view of the emotional disorders seen in some of these patients we have embarked upon the use of an assessment of anxiety and depression as a screening procedure before surgical treatment. Preliminary results[17] seem to indicate that patients with high anxiety and depression scores are likely to do badly whatever physiological abnormalities are observed.

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Quicker intraoperative colonic irrigation

S. P. Y. Kwok, J. S. Varma and A. K. C. Li

Department of Surgery, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong
Correspondence to. Professor A K. C. Li

Safe primary anastomosis of the colon is now feasible in an emergency operation for left-sided colonic obstruction with the advent of intraoperative irrigation and its refinements[1,2]. Although the technique is gaining acceptance, it can prolong operative and anaesthetic time by as much as 1 h (Reference 2). We have attempted to reduce this extra time by using larger bore delivery tubing and report here our early results.

Technique

Irrigation is performed through a 26Fr Foley urinary catheter inserted via an appendicostomy, with the effluent being collected via a large bore anaesthetic scavenging tube[2]. Normal saline solution is delivered by gravity at a pressure head of 1 m via a glycine giving set (GGS, internal diameter 5 mm) similar to that used for transurethral resection of the prostate. Intermittent antegrade manual massage of the colon, especially of the hepatic and splenic flexures, is performed to facilitate flow. Irrigation is continued until a clear return is obtained.

The results were compared with those achieved by using the conventional blood giving delivery set (BGS, internal diameter 3·5 mm).

Results

Bench-testing of the system revealed that, with a pressure head of 1 m, 4 litres of normal saline solution could be delivered in 10 min via the GGS and in 20 min via the BGS.

At operation ($n=8$), it takes 30–60 min (mean 43, s.e.m. 3·6 min) using the BGS to deliver 4–8 litres of saline solution necessary for irrigation. With the GGS we observed a noticeable reduction in the time taken to obtain clear effluent. In six patients 3–5 litres of saline solution were necessary over a period of 15–30 min for adequate cleansing (mean 24, s.e.m. 2·2 min).

Discussion

Multiple factors determine the rate of flow and hence the time to cleansing of the colon by antegrade irrigation. Many of these are unalterable in the emergency situation, e.g. the length and degree of dilatation of the colon and nature and amount of faecal material present. We have attempted to expedite irrigation by increasing the diameter of the input tubing because the rate of flow through a uniform tube is proportional to the fourth power of its radius (Poiseuille formula). This simple change has resulted in a useful reduction in operative time. It may be possible to reduce the cleansing time further by increasing the input pressures.

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Ischaemic strictures in patients treated with a low anterior resection and perioperative radiotherapy for rectal carcinoma

L. Påhlman*,
B. Glimelius† and
G. Frykholm*†

*Departments of *Surgery and*
†Oncology, University Hospital,
Akademiska Sjukhuset, S-751 85
Uppsala, Sweden
Correspondence to:
Dr L. Påhlman

In five (6 per cent) of 78 consecutive patients treated with an anterior resection for rectal carcinoma, a stenosis of the sigmoid colon just above the anastomosis was observed. Four patients had received preoperative radiotherapy over a period of 1 week to a total dose of 25·5 Gy and one patient had received postoperative radiotherapy (60 Gy) over a total of 8 weeks. The length of the stenosis varied from 4 to 120 cm. Two patients subsequently underwent reoperation with an abdominoperineal resection and three patients with a Hartmann procedure. In all patients the inferior mesenteric artery had been ligated close to the aorta. It is proposed that the stenosis may have been due to insufficient circulation in the marginal artery. This insufficiency may have been aggravated by the irradiation, as the retained part of the sigmoid colon was partly included in the irradiation target.

Keywords: Rectal carcinoma, ischaemia, irradiation, anterior resection

Anterior resection is an established surgical procedure in patients with carcinoma of the rectum and rectosigmoid[1–3]. However, in a large group of patients with rectal carcinoma, surgery alone is not sufficient and additional therapy, particularly radiotherapy, has been used. With preoperative or postoperative radiotherapy delivered to a sufficiently high dose, the local recurrence rate has decreased significantly, although there has not been any major impact on survival[4–6]. After preoperative irradiation, a low anterior resection can safely be performed, with no immediate irradiation-related complications[5,7]. However, observations after prolonged follow-up are still sparse. We present five cases of postoperative supra-anastomotic stenosis of the bowel, of different lengths, following low anterior resection. Four patients received preoperative irradiation and one received postoperative irradiation.

Patients and methods

Between October 1978 and December 1985, 122 patients underwent a curative resection for rectal carcinoma at the Department of Surgery of the University Hospital, Uppsala, Sweden. Forty-four patients were treated with an abdominoperineal resection and 78 patients with an anterior resection. In five (6 per cent) of those treated with an anterior resection, stenosis of the sigmoid colon developed above the anastomosis.

From October 1978 until October 1980, all patients with a primarily resectable tumour received preoperative radiotherapy over a period of 1 week to a total dose of 25·5 Gy[6] From October 1980 until December 1985, all patients were randomly allocated to receive either preoperative or postoperative irradiation[7] Preoperatively the dose was 25·5 Gy in 1 week, and postoperatively it was 60 Gy over 7–8 weeks with a 1–2 week interval after 40 Gy. In patients with a tumour higher than 10 cm above the anal verge, the target volume included the posterior part of the pelvic cavity from 5 cm above the anal orifice and the lower lumbar region around the aorta up to the middle of the fourth lumbar vertebra, except for the last 10 Gy of the postoperative radiation when the upper limit was below the sacral promontory. If the tumour was situated below the 10-cm level, the anal canal was also included in the target

The patients were followed up every third month during the first 2 years, twice a year up to 5 years, and then once a year. No patient has been lost to follow-up.

Case 1

A 54-year-old man with insulin-treated diabetes mellitus underwent an anterior resection in October 1981 after preoperative radiotherapy. The tumour (Dukes' C) was situated 12 cm from the anal verge The postoperative course was uneventful, but the patient had severe problems with frequent bowel movements. An X-ray examination of the colon 25 months postoperatively revealed a 4-cm stricture of the bowel just above the anastomosis. Repeated endoscopic biopsies showed no cancer but slight non-specific inflammation and submucosal fibrosis. Computed tomography over the region disclosed no signs of recurrent tumour. A sigmoidostomy was performed but the rectum was left.

Case 2

A 69-year-old previously healthy man underwent an anterior resection in June 1983 after preoperative radiotherapy The rectal tumour (Dukes' A) was situated 12 cm from the anal verge There were no postoperative complications Twenty-six months later, investigation of diarrhoea showed a supra-anastomotic stricture 4 cm long. The patient underwent an emergency Hartmann procedure. Multiple biopsies from the stenotic site showed oedema, slight fibrosis and a non-specific inflammatory reaction.

Case 3

A 63-year-old previously healthy woman with a tumour (Dukes' A) situated 6 cm from the anal verge underwent a low anterior resection after preoperative irradiation. Postoperatively an abscess developed in the rectovaginal septum, but no anastomotic leakage was found. The patient also had repeated problems with urgency postoperatively. Twenty-six months later an acute obstruction occurred and a barium enema revealed a 20-cm stenosis of the sigmoid colon just above the anastomosis (*Figure 1*). The patient underwent reoperation with an abdominoperineal resection. Macroscopically the bowel was extensively thickened and firm and histopathological examination showed extensive fibrosis in all layers with no signs of recurrent tumour.

Case 4

A 64-year-old woman was admitted in May 1985 with a rectal tumour (Dukes' B) situated 10 cm from the anal verge. After preoperative irradiation, a low anterior resection was performed. The postoperative course was uneventful. Twelve months postoperatively the patient became constipated and an X-ray examination revealed a 15-cm supra-anastomotic stricture. Reoperation was carried out with the intention of performing an abdominoperineal resection, but a huge liver metastasis was found and only a sigmoidostomy was performed. Sections from the thickened part of the sigmoid colon showed oedema and fibrosis but no cancer.

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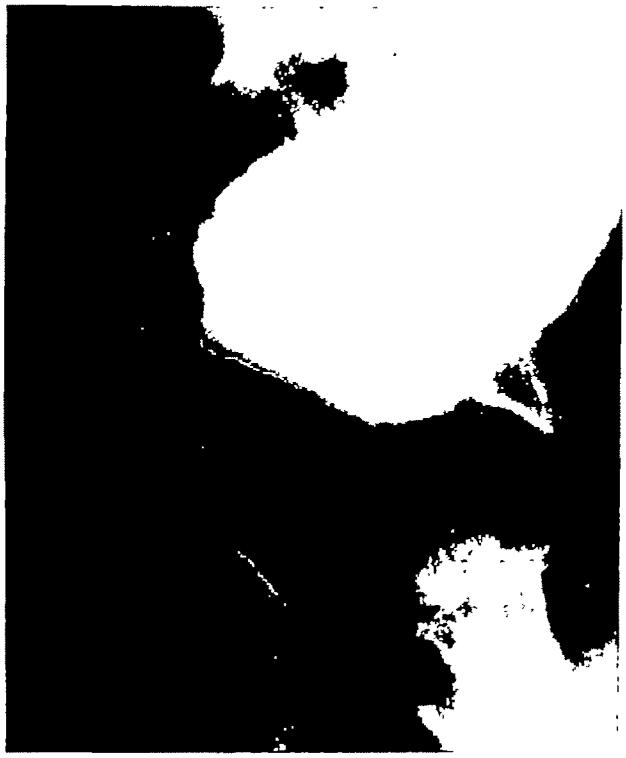

Figure 1 *Barium enema radiograph of a 63-year-old woman with an obstruction showing a 20-cm preanastomotic stenosis of the sigmoid colon*

Case 5

A 40-year-old previously healthy man with a rectal tumour (Dukes' C) situated 11 cm from the anal verge underwent an anterior resection in March 1983. As the patient was allocated to the postoperative irradiation group he subsequently received 60 Gy. The postoperative period was uneventful. In August 1985, a transverse loop colostomy was performed because of colonic ileus On X-ray examination a 7-cm supra-anastomotic stenosis was found, and 1 month later an abdominoperineal resection was undertaken. On histopathological examination no recurrent tumour was observed, but the bowel wall was extremely thick and microscopy showed fibrosis in all layers

Discussion

Anastomotic stricture is a well-known phenomenon in patients treated with an anterior resection. However, these strictures are short (0 5 cm) and (most likely) due to anastomotic leakage. Such a stricture is easy to treat with balloon dilatation. In the five cases described here, the strictures were considerably longer and there was no real suspicion of anastomotic dehiscence except in case 4. To our knowledge, there are no reports in the literature of such long stenoses following an anterior resection As all these patients received additional irradiation, and because this is a fairly new treatment in patients with rectal carcinoma, it is important to determine whether or not the stenosis described in the sigmoid colon is partly or entirely attributable to the irradiation.

The irradiation was given with a three-field technique with the patient in a prone position[8]. This technique allowed delivery of a high dose to the tumour area with relative sparing of the surrounding normal tissues. Only the distal part of the sigmoid colon was included within the target and thus received the prescribed tumour dose The proximal part of the sigmoid colon received a considerably lower dose. The part of sigmoid colon included in the 'full-dose' target was resected in the four cases where the irradiation was delivered preoperatively However, in the patient who received postoperative irradiation, the strictured part of the colon was placed within the target. Except in this latter case it is therefore unlikely that the stenosis is a direct effect of the irradiation on the affected segment of the colon. The dose was also below that usually considered necessary to cause fibrosis of the colon

Histopathological examinations of repeated biopsies from all cases and from the resected bowel in two cases showed variable fibrosis in most layers, sometimes in addition to oedema and/or non-specific chronic inflammation. There were no detectable changes indicating any specific aetiology

It is also unlikely that the strictures were due to any infectious complication, as all but one patient had an uneventful postoperative recovery. On the other hand, all patients underwent a high-tie resection, i.e. with ligation of the inferior mesenteric artery at the aorta. With such a resection the blood flow to the sigmoid colon is dependent on a well-functioning marginal artery.

It is possible that this complication is due to insufficient circulation in the marginal artery. It is also conceivable that the effect of this insufficiency may have been aggravated by the concomitant irradiation. It should be mentioned that the doses used, both preoperatively (25·5 Gy in 1 week corresponds to a dose of 46 Gy in 4–5 weeks if given in 2 0 Gy fractions) and postoperatively (60 Gy in about 8 weeks) were higher than in most reported studies, which may explain why this phenomenon has not been reported earlier[4,9–11]. On the other hand, according to experimental data, the minimal dose required to kill micrometastases with a high degree of probability is about 45 Gy given over 4–5 weeks, or a comparable dose with other fractionation schedules[12] Nevertheless, before any firm conclusions can be drawn, further reports on this complication and its relation to irradiation have to be evaluated. Whatever the mechanism, the contribution of irradiation must be explored.

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Anorectal physiology validated: a repeatability study of the motor and sensory tests of anorectal function

J. Rogers*†,
S. Laurberg*,
J. J. Misiewicz†,
M. M. Henry*† and
M. Swash*

**Department of Physiology,*
St Marks Hospital and
†Department of Gastroenterology
and Nutrition, Central Middlesex
Hospital, London, UK

Correspondence to:
Mr J. Rogers, Department of
Gastroenterology and Nutrition,
Central Middlesex Hospital,
Acton Lane, London NW10 7NS,
UK

Sixteen subjects (mean (s.d.) age 50·7 (12·8) years, three men) were studied on two separate occasions by two experienced investigators in random order. A standard protocol of anatomical, manometric and electrophysiological assessments of anorectal motor and sensory function was followed. No significant differences were found between the results obtained by the two investigators in the measurements of perineal descent, anal canal length, anal canal resting pressure and squeeze pressure, pudendal nerve terminal motor latency, single-fibre electromyography fibre density of the external anal sphincter, and thresholds of mucosal electrosensitivity. This study shows that the standard tests of anorectal sensorimotor function are repeatable by different investigators. In addition, it suggests that comparison of data obtained in different centres using these techniques is valid.

Keywords: Anorectal physiology, repeatability

Anatomical, motor and sensory tests of anorectal function have been used extensively for research into abnormalities of pelvic floor function, in particular the investigation of the pathogenesis of idiopathic faecal incontinence[1–8]. The information obtained from these tests in normal subjects has increased the understanding of the mechanism of continence, and of the pathogenesis of other forms of pelvic floor dysfunction, such as the solitary rectal ulcer syndrome[9–11] and the obstructive defaecation of young constipated women[12–15]. The tests have also been used to assess objectively the results of postanal repair[16,17] and as an adjunct to clinical assessment in the management of patients with anorectal disorders. Despite the increasing use of these techniques there has been no objective assessment of the interobserver repeatability. The aim of this study was to measure the repeatability of the standard tests of anorectal motor and sensory function.

Patients and methods

Sixteen subjects (mean (s.d.) age 50·7 (12·8) years, three men) were studied on two separate occasions by two experienced investigators (J.R. and S L) in random order. The mean delay between the two tests was 20 days (range 14–39 days). The clinical diagnosis in each subject is shown in *Table 1*. The subjects were studied in the left lateral position.

Anatomical position

The perineal position was measured in centimetres at rest and on straining to defaecate using a perineometer[18] This device measures the position of the perineum in reference to the plane of the ischial tuberosities The amount of descent was calculated by subtraction of the strain value from the rest value.

Tests of motor function

Anal manometry, functional anal canal length, and resting and maximum squeeze pressures. These were measured using a closed water-filled system consisting of a 4-mm diameter microballoon mounted on a polyethylene tube 2 mm in diameter connected to a pressure transducer (Statham Instruments Incorporated, Hato Rey, Puerto Rico) and a pen recorder (Devices®, Lectromed Ltd., Jersey, UK). The system was calibrated in centimetres of water at ambient temperature and pressure. The balloon was lubricated with K-Y jelly (Johnson and Johnson Ltd., Slough, UK) and gently inserted into the rectum, the pressure was continuously monitored as the balloon was removed in 1-cm stations. This allowed the maximum resting pressure and functional length of the anal canal to be recorded. The balloon was reinserted into the anal canal to record the maximum voluntary squeeze pressure In addition, the midanal canal resting and voluntary contraction pressures were measured.

Pudendal nerve terminal motor latency (PNTML). This was measured using a specially constructed finger-stall[4], with stimulating electrodes mounted at the tip and recording electrodes mounted at the base connected to a standard electromyographic recording machine (Neuromatic 2000-M, Dantec Ltd., Bristol, UK). The stimulator was inserted into the rectum and a supramaximal stimulus (8 3 ma, 0·1 ms) delivered to the pudendal nerve on each side. The action potential of the external anal sphincter was recorded by the base electrodes of the stimulator, allowing measurement of the latency of conduction[2].

Single fibre electromyography (EMG). Using a sterilized fine needle electrode with a recording surface of 25 μm diameter (Dantec, 13K87, Dantec Ltd.) recordings of up to 20 different single muscle fibre electrical potentials were made. Analysis of the tracings by agreed criteria allowed the calculation of the fibre density[2,19], an index of motor unit clustering – a consequence of denervation and subsequent reinnervation

Tests of sensory function

Mucosal electrosensitivity (MES)[8,20] This was measured using a specially constructed probe comprising two platinum electrodes placed 1 cm apart near the tip of a 10 Fr polyvinyl catheter graduated in centimetres. Copper wires connected the electrodes to a constant current generator (Department of Medical Physics, BESA, Bristol, UK), supplying 0 1-ms square wave stimuli at a constant rate of 5 pulses

Table 1 *Summary of patients' age, sex and clinical diagnosis*

Subject	Age	Sex	Diagnosis
A	61	M	Perineal pain
B	67	F	Faecal incontinence
C	72	F	Faecal incontinence and rectal prolapse
D	42	M	Faecal incontinence
E	52	F	Perineal pain
F	54	F	Faecal incontinence
G	26	F	Faecal incontinence
H	51	F	Faecal incontinence
I	43	F	Anterior mucosal prolapse
J	63	F	Perineal pain
K	29	M	Obstructive defaecation
L	64	F	Faecal incontinence
M	47	F	Perineal pain
N	43	F	Faecal incontinence
O	50	F	Obstructive defaecation
P	47	F	Faecal incontinence

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per second The probe was lubricated with K-Y jelly and inserted to the midpoints of the upper, middle and lower thirds of the anal canal which were determined by measurement of the functional anal canal length. The current across the electrodes was increased in steps of 0·1 ma until a threshold of sensation was reported by the patient, usually as a burning or tingling sensation. Three measurements of the threshold were made at each site and the lowest reading was recorded For the assessment of repeatability the functional anal canal length measured by the first operator was used to divide the anal canal into thirds for the second test of electrosensitivity, preventing bias due to a possible difference in assessment of functional length.

Statistics

Statistical analysis of the data for repeatability is taken from Bland and Altman[21]. The bias is the mean difference between the two methods for the measurement of the variable. The 95 per cent confidence intervals show the precision of the estimate.

Results

The results are summarized in *Table 2*.

Anatomical position

There was good agreement between the two studies for the measurement of perineal position at rest (*Figure 1*) and on straining and the degree of descent calculated from these measurements (*Table 2*).

Motor function

Manometry. The agreement between the two studies for the measurement of resting (*Figure 2*) and voluntary contraction pressures showed insignificant bias of −9 and −10 cmH_2O, respectively The 95 per cent confidence intervals, however, were large from −25 to 4·7 cmH_2O for resting pressure and from −32 to 14 cmH_2O for voluntary contraction pressure. Agreement for midpoint anal canal pressure showed a bias of −7 cmH_2O (95 gper cent confidence interval from −16·3 to 2·3) at rest and 1·5 cmH_2O (from −26·1 to 29·1) on voluntary contraction.

Electromyography. The bias for the electromyographic tests of PNTML (*Figure 3*) and calculation of fibre density (*Figure 4*) were very small and agreement was excellent. Repeatability for the calculation of fibre density derived from single muscle fibre EMG studies was assessed by arranging for each investigator to analyse the other's coded tracings, so that the identity and diagnosis was unknown. Agreement was excellent: bias −0·003, 95 per cent confidence interval from −0·07 to 0·06.

Sensory function

Agreement between the two studies for thresholds to mucosal electrostimulation in the anal canal were excellent with insignificant bias (*Figure 5*).

Discussion

This is the first objective assessment of the repeatability of the standard tests of anorectal sensorimotor function. In this study these standard tests showed a high degree of repeatability when two independent investigators, experienced in the techniques, examined the same subjects on separate occasions.

Manometry, although repeatable in terms of calculated bias, had large 95 per cent confidence intervals. In terms of precision, manometry was the least repeatable of all the tests. Pressure measurement at the midpoint of the anal canal did not improve the degree of agreement. This is an important observation as manometric assessment is the most commonly used test of motor function. The variation may be due to normal day-to-day variation in pressure in the anal canal, to differences in patient compliance or to differences in the technique used by the investigators.

In contrast, single-fibre EMG and PNTML tests were highly repeatable with very narrow limits of agreement and confidence intervals, indicating good precision. This finding supports the use of single-fibre EMG fibre density and PNTML measurements in addition to manometric tests of anorectal motor function.

Mucosal electrosensitivity was highly repeatable which is an interesting finding as the thresholds depend on the response of the subject to a perceived stimulus, in contrast to the tests of motor function which are objective Other tests of sensation in

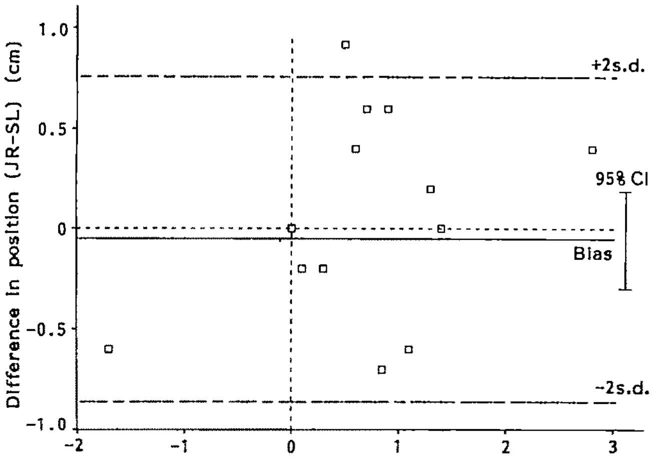

Figure 1 *Agreement between the two investigators for perineal position (rest) The confidence interval (CI), bias and ±2 s d. are shown*

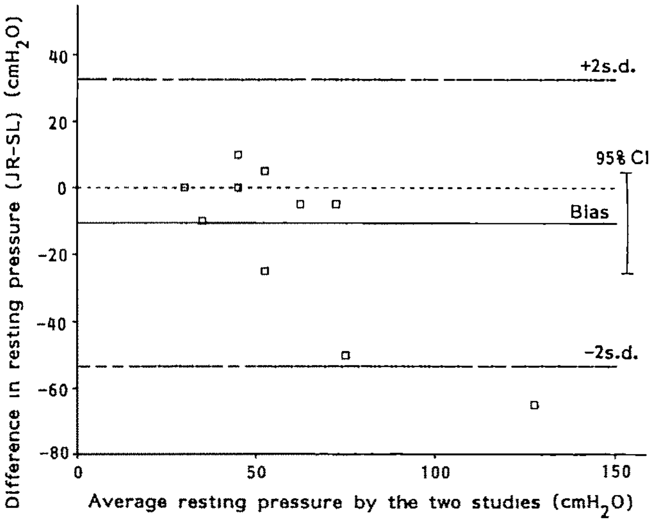

Figure 2 *Agreement between the two investigators for resting pressure The confidence interval (CI), bias and ±2 s d are shown*

Table 2 *Summary of results*

	Bias	95% confidence intervals	2 s.d	Range
Perineal descent (cm)	−0·07	−0·47 to 0·31	1·3	0·5–2·4
Anal canal length (cm)	−0·1	−0·2 to 0·4	1·0	2–4
Resting pressure (cmH_2O)	−10	−25 to 4·7	42	30–130
Squeeze pressure (cmH_2O)	−9	−32 to 14	65	40–250
Pudendal nerve latency (ms)	0·1	−0·3 to 0·2	0·6	1·7–2·7
Fibre density	0·26	−0·04 to 0·57	0·35	1·83–2·58
Mucosal electrosensitivity (ma)	0·5	−3·3 to 4·3	19·0	1·75–23·6

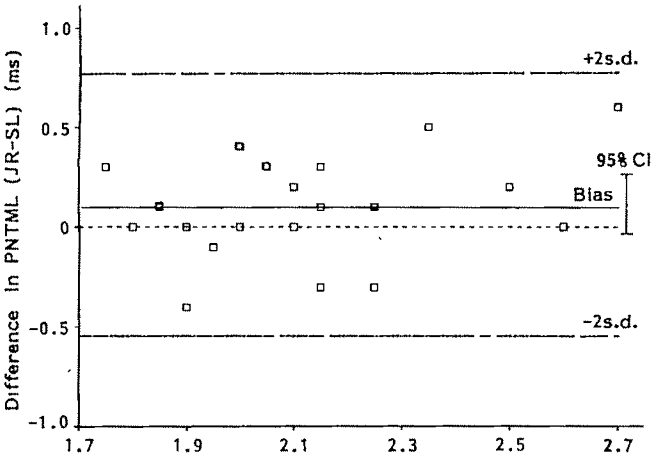

Figure 3 *Agreement between the two investigators for pudendal nerve terminal motor latency (PNTML) The confidence interval (CI), bias and ±2 s d are shown*

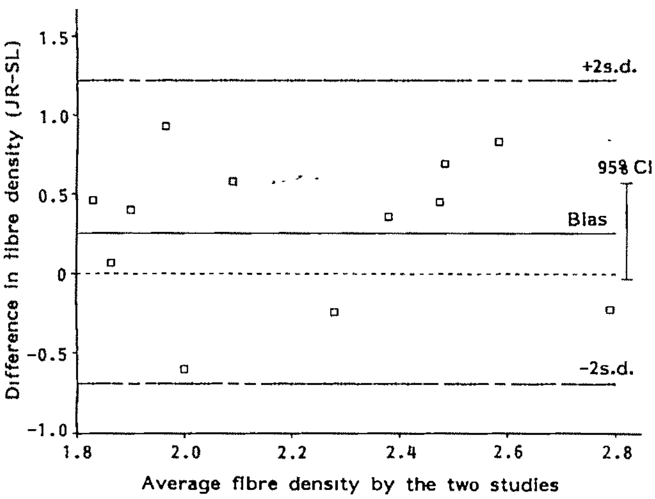

Figure 4 *Agreement between the two investigators for fibre density The confidence interval (CI), bias and ±2 s.d. are shown*

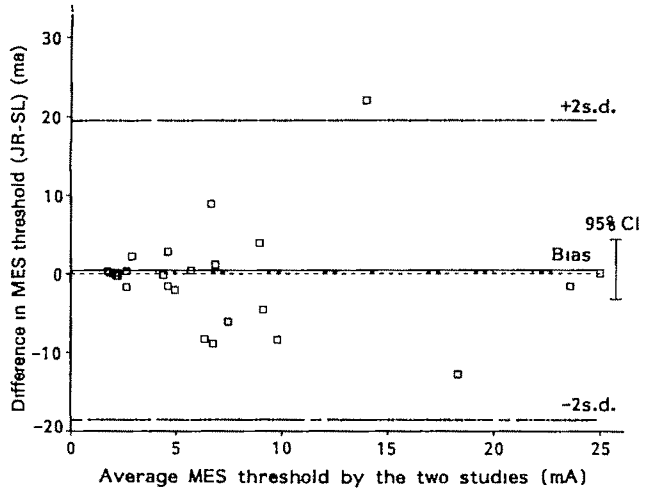

Figure 5 *Agreement between the two investigators for mucosal electrosensitivity (MES). The confidence interval (CI), bias and ±2 s.d are shown*

the anorectum are available such as temperature sensitivity[22] of the anal canal or balloon distension of the rectum[8], but these are either too complicated (temperature), or too unreliable (rectal distension)[8,23] for routine use.

The sensorimotor tests of anorectal physiology used in this study are quick and easy to perform, a full test taking approximately 35 min. The equipment is standardized and readily available. This study shows that the standard tests of anorectal sensorimotor function are repeatable by different investigators. In addition, it suggests that comparison of data obtained in different centres using these techniques is valid.

Acknowledgements

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Management of infection after prosthetic abdominal rectopexy (Wells' procedure)

A. H. McL. Ross and J. P. S. Thomson

St. Mark's Hospital for Diseases of the Rectum and Colon, London, UK
Correspondence to:
Mr A H. McL. Ross, Surgical Unit,
Broomfield Hospital, Broomfield,
Chelmsford, Essex CM1 5ET, UK

The management and results of treatment of eight cases of implant infection after a Wells' rectopexy for rectal prolapse are reported. Most infections presented within 3 months of the rectopexy. Fever, abdominal or pelvic pain, diarrhoea, and the passage of pus per rectum were common presenting features. Removal of the infected implant per rectum or per vaginum was successful in four of five attempts and is the recommended initial approach, particularly in cases occurring early after surgery. Despite removal of the implant early after rectopexy recurrent prolapse did not occur.

Keywords: Rectal prolapse, infection, rectopexy

Since 1959 when Wells described an abdominal rectopexy using a prosthetic implant for the management of full-thickness rectal prolapse it has proved to be a popular and safe method of management[1]. Its efficacy in preventing recurrent prolapse has been proved in a number of published series[2–6]. Furthermore, the operation is relatively simple to perform compared with those previously employed and is well tolerated even in a population that includes many patients who are aged and infirm.

The most serious potential postoperative problem is infection of the synthetic implant. Such an event is unusual but necessitates the removal of the implant and may result in considerable morbidity. Little published evidence exists about the mode of presentation, treatment and long-term consequences of such infection. This paper reports eight such patients who were referred to and treated at St. Mark's Hospital and reviews previous published experience

Patients and methods

Eight patients treated for infected implants after posterior rectopexy are reviewed Three patients had the rectopexy carried out at St. Mark's Hospital, representing all identified implant infections after rectopexy at this hospital The remainder were operated on elsewhere.

Polyvinyl alcohol sponge was implanted in seven of the patients and Mersilene® (Ethicon Ltd., Edinburgh, UK) mesh in one. All three patients treated initially at St. Mark's Hospital received perioperative antibiotic cover, generally gentamicin and metronidazole. Case records and X-rays were examined and each patient was interviewed. Presenting symptoms and signs, treatment and postoperative progress, with particular reference to continence, the presence of anal discharge and any recurrence of prolapse were assessed

Results

A summary of the features of each patient is presented in *Tables 1* and *2*. Follow-up ranged from 3 months to 9 years. Symptoms developed from 1 week to 6 years after operation and had been present for between 10 days and 20 months before treatment. Pelvic pain, fever, and the discharge of pus per vaginum or per rectum were common features at presentation.

On rectal examination, pelvic induration, a palpable mass and tenderness were usual At sigmoidoscopy two patients had visible sinuses entering the rectum (*Figure 1*). A perirectal cavity was demonstrated by contrast enema in three cases (*Figure 2*). In three patients who developed rectal strictures, infection had been present for a prolonged time (6–18 months) before implant removal Two of these patients had diarrhoea and one required rectal excision. The other patient's diarrhoea (No 2) and stricture resolved after removal of the prosthesis although she remains occasionally constipated.

Two cases had developed a ureteric stricture and presented with back pain in one case and urinary frequency in the other. Both were confirmed by intravenous urography. In patient No. 5 the problem settled after removal of the prosthesis. In No 1 ureterolysis was performed successfully.

Five implants were removed per rectum or per vaginum. In general, artery forceps were used to enlarge any sinus present thus allowing removal of the implant *in toto* or piecemeal If no sinus was present a formal posterior proctotomy was made over the inflammatory mass to allow implant removal. In one case the implant was removed using an intersphincteric approach. In one patient (No. 6) the implant was removed per rectum after it proved impossible to remove it at laparotomy when a Hartmann's operation was performed. In patient No 1, piecemeal, incomplete removal only was achieved after three operations and the patient has undergone rectal excision because of persistent sepsis and stricture.

The implant was removed at laparotomy in a further three patients, one of whom (No. 4) developed a postoperative ureterocutaneous fistula treated by nephrectomy.

At the time of writing, three patients have colostomies. The other five patients without colostomies consider themselves continent of solid stool and none has developed recurrent prolapse. One patient (No. 4) continues to complain of low grade non-specific abdominal pain.

Discussion

Transabdominal rectopexy using an implant sponge or mesh is a safe, effective and popular operation for full-thickness rectal prolapse[2–7] Serious complications are uncommon despite the often frail state of patients who undergo the operation. In Wells' original description, polyvinyl alcohol sponge was used and since then polypropylene mesh, polytetrafluoroethylene sheet, and Mersilene mesh have all been used as alternatives. Boulos *et al.*[8] have recently suggested that if patients can be followed for long enough a high rate of prolapse is associated with the use of polyvinyl alcohol sponge[9] rectopexy. Suturing the mobilized rectum directly to the presacral fascia without insertion of an implant, avoids the risk of infection and appears to be effective in controlling prolapse[7,10].

Implant infection is an infrequent complication with an incidence variously reported between 0 and 16 per cent[2–6,11] Infection is either the result of endogenous infection after inadvertent breach of the rectal lumen or exogenous infection The presence of a postoperative pelvic haematoma may encourage such infection. Prosthetic sepsis usually presents early after rectopexy. In this series, six of eight patients developed symptoms within 3 months of operation, although

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Table 1 *Patient details and symptoms*

Patient No.	Age	Sex	Time to onset of symptoms after rectopexy	Duration of symptoms	Symptoms
1	53	M	2 years	18 months	Sacral pain, rectal discharge, fever
2	69	F	1 week	6 months	Diarrhoea, pus per rectum
3	69	F	3 weeks	10 days	Fever, pelvic pain, vomiting
4	78	F	1 week	3 weeks	Fever, pelvic pain, vomiting
5	70	F	2 weeks	8 months	Abdominal pain, pus per rectum and per vaginum, urine frequency
6	62	F	7 weeks	20 months	Pus per rectum, rigors, incontinent
7	76	F	6 years	6 months	Diarrhoea, pain in coccyx, incontinent
8	69	F	3 months	6 weeks	Pelvic pain, pus per rectum

Table 2 *Signs, type of operation and outcome in the eight patients with infected implants*

Patient No.	Findings	Operation	Follow-up	Current status
1	Induration, sinus per rectum, rectal stricture, left ureteric obstruction	Sinus enlarged, implant removal per rectum × 3, abdominoperineal excision	1 year	Colostomy
2	Stricture, induration	Implant removal at laparotomy	6 years	Asymptomatic, continent
3	Mass per rectum, tender per rectum	Intersphincteric excision of implant	3 years	Asymptomatic, continent
4	Tender per rectum	1. Laparotomy, drain pelvic abscess and remove implant 2. Left nephrectomy	9 years	Abdominal pain, constipation continent
5	Pelvic induration, pus per vaginum and per rectum, left ureteric ostruction	Implant removal per vaginum	3 months	Anal discharge, continent
6	Induration per rectum	1. Hartmann's operation 2. Implant removal per rectum	8 months	Anal discharge
7	Pus per rectum, sinus per rectum, stricture	Abdominoperineal excision	1 year	Asymptomatic
8	Pus per rectum, induration	Implant removal per rectum	1 year	Asymptomatic, continent

Polyvinyl alcohol sponge was used in all patients except No. 7 in whom Mersilene mesh was used

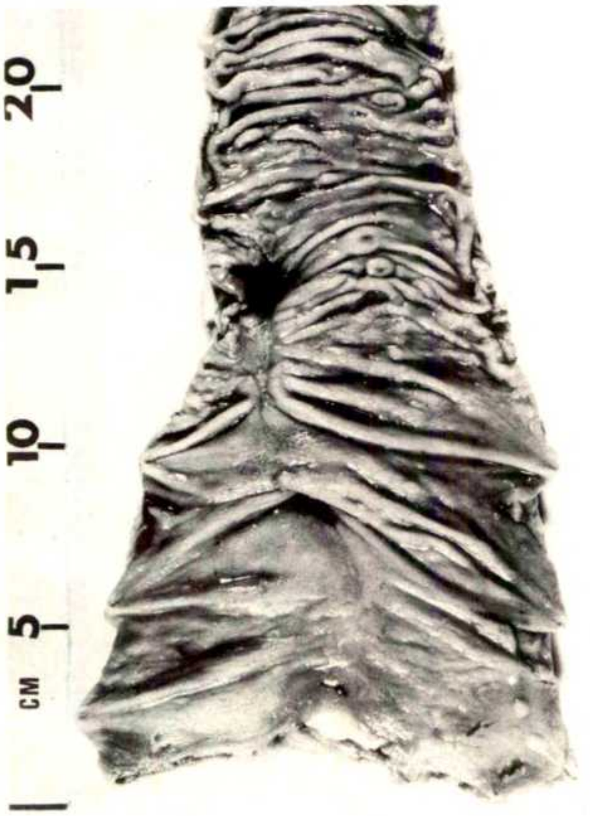

Figure 1 *The specimen from patient No. 7 demonstrating the presence of two sinuses into the rectum from the infected polyvinyl alcohol sponge implant*

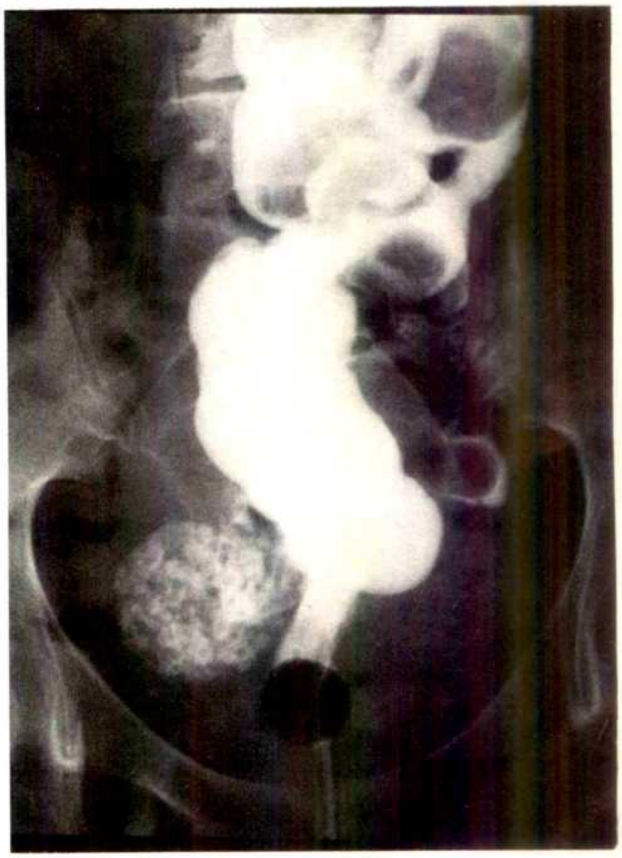

Figure 2 *A contrast enema in patient No. 6 before treatment showing an extensive perirectal cavity*

symptoms had been present for much longer before eventual treatment. Pelvic pain, fever, discharge of pus per rectum or per vaginum and diarrhoea are common features and should alert the clinician to the possibility of implant infection if they occur postoperatively.

On examination there may be a fever, and digital rectal examination reveals perirectal tenderness and induration. Pus may be seen in the lumen of rectum and vagina, and a visible sinus may be present. In this series a contrast enema revealed a perirectal cavity in three patients, although only one had a visible sinus on sigmoidoscopy. A contrast enema should not be required routinely.

Opinion is divided on the optimum method of removal of the infected implant. Of 13 cases reported in the literature, most (ten) have been managed by removal at a further laparotomy, some authors commenting on the ease with which this was achieved. Lake *et al.*[11] have suggested removal at laparotomy particularly in those cases where sepsis is long established. Our results suggest that such a policy may be unnecessary, technically difficult, and hazardous to surrounding viscera. Two of our cases, managed by laparotomy, were complicated by operative damage to adjacent viscera and, in both, sepsis had been present for a considerable time before operation. In contrast, particularly when the septic complication had been present for a short period, removal per rectum or per vaginum was, in general, simple to achieve and atraumatic. Such an approach was adopted with success in three of four cases of infection recorded by Morgan *et al.*[2], two of which occurred within 3 weeks of the initial rectopexy.

Although no trials comparing infection rates using different implant materials exist, it is interesting to note that the use of polypropylene has been associated with no complicating infection[6]. Lack of published detail on the use of prophylactic antibiotics prevents any accurate assessment of their value in preventing implant infection[2,5,11]. Nevertheless, in achieving a zero infection rate after rectopexy using polypropylene mesh, Keighley *et al.*[6] employed a 24-h regimen of wide spectrum antibiotics and it is our practice always to administer such a regimen (aminoglycoside and metronidazole) when an implant has been used.

The absence of recurrent prolapse, even when the implant was removed soon after surgery, confirms others' experience[2,5]. This presumably reflects the effect of perirectal fibrosis induced by infection, and encourages early removal of the implant after the diagnosis of infection has been made. Continence appears to be unaffected by this complication.

Avoidance of contamination and pelvic haematoma by meticulous surgical technique is clearly the priority in management. If infection does occur, the diagnosis should be recognized early. This will often allow transrectal or transvaginal removal of the implant and avoid an unnecessary laparotomy.

Acknowledgements

We would like to thank the surgeons of St. Mark's Hospital for their permission to report these cases.

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Anal and ileal pouch manometric measurements before ileostomy closure are related to functional outcome after ileal pouch–anal anastomosis

N. A. Scott,
J. H. Pemberton,
D. C. Barkel and
B. G. Wolff

Section of Colon and Rectal Surgery, Department of Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA
Correspondence to:
Dr J. H Pemberton, 200 First Street Southwest, Rochester, Minnesota, 55905, USA

Anal canal length, anal canal resting and squeeze pressures, ileal pouch capacity and pouch compliance were measured in 104 patients after ileal pouch–anal anastomosis but before ileostomy closure. The intention was to determine if such parameters were associated with late functional outcome after re-establishment of intestinal continuity. Functional outcome in terms of stool frequency (day and night), incontinence (day and night), perianal pad use, perianal skin irritation, and the use of constipating agents was assessed for all 104 patients 1 year or more (median 438 days) after ileostomy closure. A low mean anal sphincter resting pressure before ileostomy closure was associated with subsequent nocturnal incontinence ($P < 0{\cdot}05$) *and, to a lesser extent, the need to use constipating agents* ($P = 0{\cdot}08$). *Pouch compliance if low before ileostomy closure was associated with an increased frequency of nocturnal stool frequency after 1 year* ($P < 0{\cdot}05$). *Anal canal length, anal sphincter squeeze pressure and pouch capacity before ileostomy closure were not related to subsequent functional outcome in these patients.*

Keywords: Anorectal manometry, ileal pouch–anal anastomosis, functional outcome

Removal of the entire colonic mucosa, and hence its malignant potential, is an established part of the management of patients with chronic ulcerative colitis and familial adenomatous polyposis. Proctocolectomy in these patients has been increasingly followed by anastomosis of an ileal pouch to the anus[1]. Patient satisfaction with this restorative procedure is extremely high[2]. However, a proportion of patients with an ileal pouch–anal anastomosis are persistently troubled by excessive stool frequency and episodes of minor and major incontinence. We wished to determine if there were any factors that could be quantified early, before re-establishment of intestinal continuity, which might be associated with late pouch function. Therefore, we measured anal canal pressures at rest and on squeezing, pouch capacity and pouch compliance in 104 patients with an ileal pouch–anal anastomosis before closure of the ileostomy. Our purpose was to determine whether there was a correlation between the measurements of anal canal and reservoir function and functional status of the patients 1 year or more after ileostomy closure.

Patients and methods

Patients

All patients who had a diverting ileostomy closed after an ileal pouch–anal anastomosis at the Mayo Clinic between January 1984 and June 1986 were considered eligible for this study. This period was chosen to ensure at least 1 year of follow-up for each patient after ileostomy closure. In addition, the manometry technique used during this time was performed in a uniform manner using a perfused probe.

Ileal pouch–anal anastomosis was performed in all patients according to the technique described by Ballantyne *et al*[3]. A short (3–5 cm) rectal muscular cuff was retained in each patient and no patient underwent rectal mucosal excision using the eversion technique

Clinical outcome was recorded for each patient in standard fashion Details ascertained included stool frequency during the day and night, incontinence (day and night), the use of pads, perianal irritation, and the continued use of the constipating agents loperamide and diphenoxylate hydrochloride

Before ileostomy closure, each patient had anal manometry and the pouch volume and compliance were measured A rigid 1·2-cm diameter polyglass probe with four perfused ports oriented 90° apart was used to measure radial pressures in the anal canal The probe was inserted into the ileal pouch transanally and was then withdrawn using a 1-cm station pull-through technique as described by Heppell *et al*[4]. In this way, the length of the canal was determined. Resting pressures at each level were recorded along the length of the anal canal. The procedure was repeated but with the patient squeezing on the probe at each 1-cm interval The highest basal pressure recording in each patient was designated the maximum resting pressure, and averaging the recorded resting pressures gave the mean resting pressure. The maximum and the mean squeeze pressures were derived similarly. For each patient, therefore, five manometric measurements were recorded: anal canal length, mean resting pressure, maximum resting pressure, mean squeeze pressure and maximum squeeze pressure.

On completion of anal manometry, a 12-cm-long flaccid latex rubber balloon attached to a small tube (outside diameter 2·6 mm) was inserted into the ileal pouch. The balloon was then inflated with air in increments of 10 or 20 ml This was continued until the patient complained of pelvic discomfort or a strong urge to evacuate. The volume of air in the balloon at this point was taken as the maximum ileal pouch capacity The pressure in the balloon when maximum ileal pouch capacity was reached was used to calculate pouch compliance in millilitres per millimetre of mercury (e.g 120 ml/60 mmHg = 2·0 ml/mmHg).

Statistical analysis

From the anal manometry and pouch measurements seven variables were determined: anal canal length, mean and maximum resting pressures, mean and maximum squeeze pressures, pouch capacity, and pouch compliance A total of seven factors measured outcome after ileostomy closure: these were stool frequency (day and night), incontinence (day and night), use of pads, perianal irritation, and use

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of loperamide and diphenoxylate hydrochloride. Linear regression analysis was used to determine statistically significant associations ($P < 0·05$) between the manometry and pouch measurements and the measurements of clinical outcome.

Results

A total of 307 patients were identified as having had a diverting ileostomy closed after an ileal pouch–anal anastomosis. Of these, 104 (*Table 1*) were referred for measurement of anal canal pressures and pouch capacity and compliance before ileostomy closure as part of a routine preoperative evaluation, which also included pouchography. No patient was referred for evaluation of a perceived problem with the pouch or anal sphincters. The median follow-up period for these patients after ileostomy closure was 438 days (range 319–1101 days)

The 104 patients studied were virtually identical to the 203 patients not studied in terms of age distribution, sex, colonic pathology, type of ileal pouch, and the incidence of postoperative complications. Clinical outcome for the 104 patients studied and the 203 other patients was also similar in terms of stool frequency, incidence of incontinence, and the use of pads and constipating medication. Perianal irritation, however, was more common in the 104 patients studied than in the 203 other patients, but this difference did not reach statistical significance (55 per cent *versus* 36 per cent, $P > 0·05$)

Stool frequency

Daytime. The length of the anal canal and anal canal resting and squeeze pressures were similar in patients with both a high daytime stool frequency (seven or more) than those with a lower daytime stool frequency (six or less). Pouch capacity before ileostomy closure was, if anything, slightly higher in patients who subsequently had the most frequent daytime stool passage Pouch compliance, however, was slightly lower in the latter patients than in those patients with less frequent daytime bowel movements. None of these differences was of statistical significance.

Night-time. Anal canal length was similar in patients with few stools at night (one or less) and in patients with more frequent nocturnal stools (two or more). Anal sphincter pressures and pouch capacity were slightly higher in those patients who passed few stools at night, but these differences were not significant. By contrast, pouch compliance before ileostomy closure was significantly higher in patients with few night-time stools (median 2·3 ml/mmHg) than in those with more frequent nocturnal bowel movements (median 1·8 ml/mmHg, $P < 0·05$; *Figure 1*).

Table 1 *Clinical and surgical characteristics of the 104 study patients*

	Number	Per cent
Sex		
Men	55	53
Women	49	47
Age (years)		
Mean	(30)	
Range	(12–51)	
Pathology		
CUC	90	87
FP	13	12
Other	1	1
Pouch		
J	102	98
Other	2	2
Diverting ileostomy		
Loop	103	99
Brooke	1	1

CUC, chronic ulcerative colitis, FP, familial polyposis

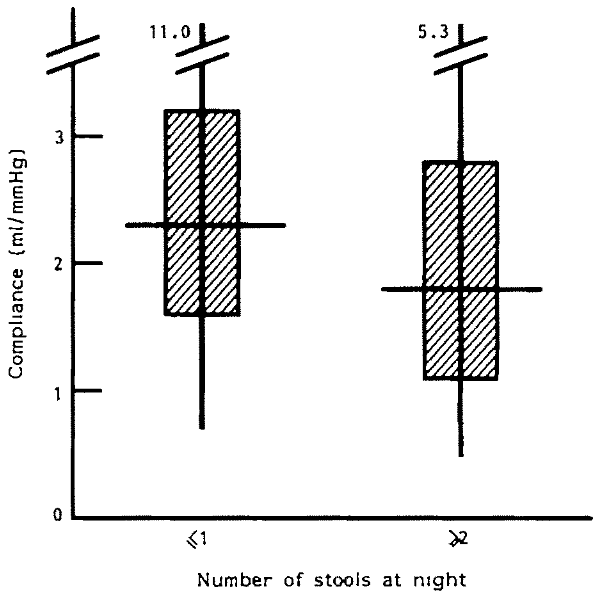

Figure 1 *Pouch compliance (volume/pressure at maximum capacity)* versus *night-time stool frequency. Median, interquartile range and range are shown Patients with one stool or less at night at follow-up had more compliant pouches before closure of the ileostomy than patients with two or more stools at night* ($P < 0·05$)

Incontinence

Daytime. The majority of patients (81 per cent) in this series had perfect daytime continence; only a single patient had frequent daytime incontinence. The length of the anal canal was not related to the frequency of daytime incontinence. Anal sphincter pressures were higher in patients with perfect continence than in patients with occasional incontinence, but not significantly. Pouch capacity before ileostomy closure was marginally greater in patients with subsequent incontinence than in patients with perfect continence, while pouch compliance did not differ between groups.

Night-time. Occasional incontinence at night was more common (40 per cent *versus* 17 per cent) than during the day. Anal sphincter pressures in general tended to be higher in patients who were continent at night; this difference was statistically significant only for the mean resting anal canal pressure ($P < 0·05$, *Figure 2*). Pouch capacity before ileostomy closure was similar in patients who were continent and in those who were incontinent. Pouch compliance did not differ between patients with no incontinence and those with either occasional or frequent nocturnal incontinence.

Pads, perianal irritation and constipating agents

The length of the anal canal was not related to the use of pads, the presence of perianal skin irritation or the use of constipating agents. However, anal canal resting pressures tended to be higher in patients who did not wear pads, did not report perianal skin irritation, and did not require constipating agents. The higher mean resting anal canal pressures seen in patients who did not need constipating medication failed to reach statistical significance ($P = 0·08$; *Figure 3*). Anal sphincter squeeze pressures were similar in patients who did or did not use pads, those with or without perianal skin irritation, and in patients who did or did not take hypomotility agents. Similarly, pouch capacity and pouch compliance before ileostomy closure showed little association with the use of pads, perianal skin irritation and the need for constipating medication.

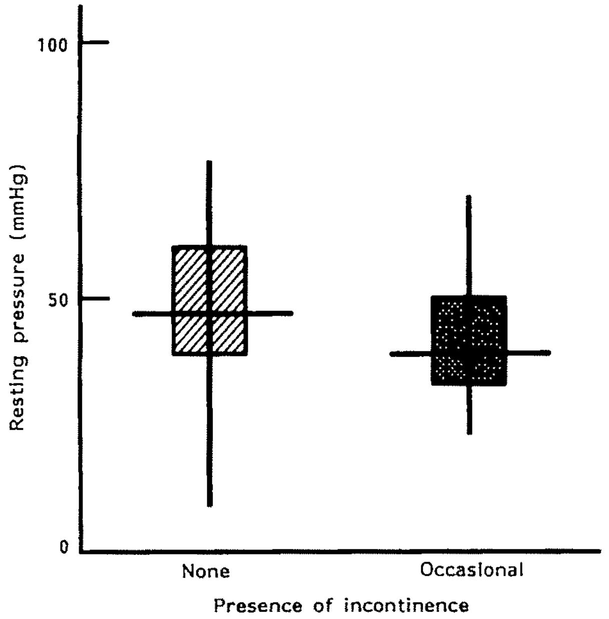

Figure 2 *Anal canal resting pressure* versus *night-time incontinence. Median, interquartile range and range are shown. Patients with no night-time incontinence at follow-up had higher resting pressures before ileostomy closure than patients who had occasional incontinence* ($P < 0{\cdot}05$)

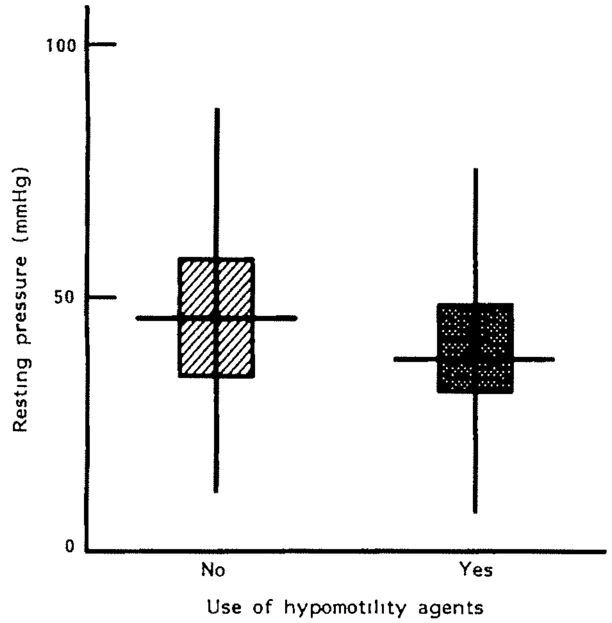

Figure 3 *Anal canal resting pressure* versus *use of hypomotility agents. Median, interquartile range and range are shown. Patients who did not use hypomotility agents at follow-up tended to have higher resting pressures before ileostomy closure than patients who did* ($P = 0{\cdot}08$)

Discussion

Patient dissatisfaction after ileal pouch–anal anastomosis is the result primarily of frequent and/or inappropriate discharge of stool. While the total stool volume presented to the pouch during 24 h is important in determining stool frequency[5], anal canal pressures and properties of the ileal pouch itself are likely to have key roles in determining clinical outcome[6,7]. This study examined these two factors, which were measured before closure of the diverting ileostomy, to determine if they correlated with pouch function 1 year after ileostomy closure.

Anal canal squeeze pressures measured before ileostomy closure in this study were not correlated with incontinence, pad use, perianal skin irritation or the need for constipating medication more than 1 year after ileostomy closure. By contrast, low mean anal sphincter resting pressure was associated with nocturnal incontinence and, to a lesser extent, with the use of constipating agents after ileostomy closure. Others have also described minor faecal leakage after ileoanal anastomosis as being a consequence of reduced resting anal pressures[8]. Resection of the rectal mucosa and/or the associated anal dilatation may be responsible for this diminution in resting anal canal pressures; avoiding this latter type of proctectomy significantly reduces the minor leakage reported by patients after conventional ileal pouch–anal anastomosis[8]. These observations, however, have been disputed recently by Keighley *et al.*[9].

The capacity of the ileal pouch measured after ileostomy closure is clearly related to pouch function assessed at the same time[5,6,10,11]. In contrast, the volume of the unused ileal pouch, as measured in this study and by Becker and Raymond[11], before ileostomy closure does not correlate with late stool frequency. This latter finding would be difficult to explain if, as has been suggested, the intraoperative volume of the double loop ileal reservoir (J pouch) is not significantly different from the volume of the reservoir measured 12 months after ileostomy closure[10]. However, the volume of an ileal J pouch does expand rapidly after ileostomy closure[11]; this explanation would then account for the absence of correlation between pouch volume before ileostomy closure and pouch function 12 or more months after ileostomy closure.

Evidence of an association between compliance of the pouch after ileostomy closure and daily stool frequency is, at best, equivocal. While one study reported an inverse correlation between frequency of defaecation and pouch compliance[6], others have failed to find the same relationship between pouch compliance and pouch function[5]. In contrast, a finding in this study was that night-time stool frequency more than 1 year after ileostomy closure was associated with pouch compliance measured before ileostomy closure. This result is similar to that reported previously for 22 patients with an ileoanal anastomosis followed for 1 month after ileostomy closure[4].

The apparent association between preclosure pouch compliance and subsequent stool frequency and the irrelevance of preclosure pouch capacity to the same outcome is of interest. Much ingenuity has been devoted to developing a pouch which achieves a large intraoperative volume[10]. However, if it is pouch compliance that is important to stool frequency after an ileal pouch–anal anastomosis, and not capacity[12], this latter approach may be a faulty one, that is, investigators should be more concerned with improving pouch compliance and not merely capacity. Whether or not pouch 'compliance' is a fixed property of the ileal wall or is amenable to changes in pouch design[6] requires further study.

In summary, we examined the relationship between measurements of anorectal manometry, pouch capacity and compliance obtained before ileostomy closure and the clinical outcome 1 year later for 104 patients with an ileal pouch–anal anastomosis. Anal canal length, anal squeeze pressures and pouch capacity before ileostomy closure were not related to late functional outcome in these patients In contrast, low anal sphincter resting pressures postoperatively were associated with nocturnal incontinence, while low pouch compliance was associated with increased nocturnal stool frequency. The results of this exploratory analysis suggest, firstly, that further prospective studies controlling for confounding variables are warranted and, secondly, that modifications of surgical technique which minimize stretch of and trauma to the anal sphincter apparatus and increase pouch compliance also require further investigation.

Acknowledgements

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Technique of laparoscopic appendicectomy

P. F. Leahy

Department of Surgery, Hant's Regional Hospital,
Windsor, Nova Scotia, Canada
Correspondence to: Dr P F. Leahy, Box 2320,
Windsor, Nova Scotia, BON 2TO, Canada

Recently laparoscopic surgery has found numerous therapeutic indications. Its many advantages over laparotomy have prompted its use by gynaecologists. This article presents a technique for appendicectomy using operative pelviscopy.

Patients and methods

Four patients with appendicitis were offered laparoscopic appendicectomy. The procedure was explained to the patients who agreed to have surgery performed by the laparoscopic technique

The procedures were performed under general anaesthesia After skin preparation, a Surgineedle® (US Surgical Corporation and Auto Suture, Connecticut, USA) was introduced in an infraumbilical position and CO_2 was insufflated slowly using a CO_2 insufflator (Karl Storz, Culver City, California, USA) A trocar and laparoscope were inserted through the infraumbilical wound and the clinical diagnosis was confirmed Using transabdominal illumination by the laparoscopic light source, the inferior epigastric vessels were identified and avoided when inserting a 5-mm trocar through a separate incision, and a second trocar, 11 mm in size, was inserted above the anterior superior iliac spine Through the respective trocar a grasping forceps and Filshie clip (Karl Storz) applicator were inserted The appendicular artery and the base of the appendix were each ligated with Filshie clips After division of the appendix it was extracted through the trocar without contamination of the wounds If the wounds required closure they were closed with 3 × 0 plain catgut Marcain® (Winthrop, Aurora, Ontario, Canada) 0·5 per cent was infiltrated as a matter of routine The patients were generally fit for discharge the following day. There were no complications in this series and the patients returned to work or normal activities within 1 week

Discussion

Laparoscopic appendicectomy can be performed with minimal morbidity[1]. In the hands of skilled laparoscopic surgeons the procedure can be performed within 10 min and when combined with regional anaesthesia can allow the very early discharge of the ambulatory patient. The presence of an acute appendix in a retrocaecal position makes the procedure a more difficult operation. The training of surgeons in this technique poses obvious difficulties, as very few general surgeons have expertise in operative pelviscopy. The advantages of laparoscopic appendicectomy over laparotomy are numerous. With thermocoagulation, haemostasis is achieved easily Using bipolar coagulation the risk of thermal injury to the surrounding organs is reduced The absence of postoperative adhesions is important especially in female patients.

This technique is relatively simple, fast and safe in the hands of experienced laparoscopic surgeons and could set a precedent for modern ambulatory surgery.

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External and internal anal sphincter responses to rectal distension in normal subjects and in patients with idiopathic faecal incontinence

J. J. Bannister*, N. W. Read, T. C. Donnelly and W. M. Sun

**Department of Surgery and Sub-department of Human Gastrointestinal Physiology and Nutrition, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK*

Correspondence to:
Professor N. W. Read

The responses of the external anal sphincter and the internal anal sphincter to rectal distension were studied in 18 female patients who had idiopathic faecal incontinence with perineal descent and 11 female control subjects, by measuring pressures at six sites within the anal canal and the electrical activity of the external sphincter. The pressure profile in the normal anal canal, at rest, was asymmetric with the highest pressure recorded in the outermost channels. Rectal distension caused a transient increase in the activity of the external sphincter, which was associated with an increase in anal pressure, particularly in the outermost two channels. This was followed by a symmetrical reduction in anal pressure throughout the anal canal, caused by relaxation of the internal sphincter and shortening of the high-pressure zone. Two patterns of response were observed in the patients with idiopathic incontinence. Twelve patients (group 1) showed normal anal relaxation, but the maximum anal pressures recorded during rectal distension or a conscious squeeze were abnormally low, suggesting weakness of the external anal sphincter. The remaining six subjects (group 2), who were older than the group 1 patients, had much lower resting pressures and showed only external sphincter contraction in response to rectal distension, with no obvious internal sphincter relaxation. However, the maximum pressures recorded during a conscious contraction of the external sphincter were lower in this group than in the normal control subjects. These results suggest that group 2 patients have impaired internal anal sphincter tone, as well as external anal sphincter weakness. This may explain why all except one of the group 2 patients, compared with only 17 per cent of group 1 patients, reported incontinence to both solids and liquids.

Keywords: Faecal incontinence, anus

Incontinence to faeces is prevented by the resistance of the anus to the passage of rectal contents. This is made up of two components, the smooth muscle of the internal anal sphincter and the striated muscle of the external anal sphincter. Distension of the rectum relaxes the internal sphincter[1] with a concomitant reduction in anal canal pressure. This response has been called the rectoanal inhibitory reflex and appears to be mediated by the enteric nerves. Anal relaxation, in response to rectal distension, is often associated with a compensatory contraction of the external sphincter. This contractile response has been called the 'inflation reflex'[2] and, while it may be a true spinal reflex, it is heavily modulated by conscious mechanisms[3].

It is technically difficult to separate the components of the anal sphincter mechanism, because the smooth muscle of the internal sphincter and the voluntary muscle of the external sphincter have a large degree of anatomical and functional overlap. Schuster *et al.*[4] attempted to record from the two muscles, by siting two balloons in the anal canal: the inner balloon recording predominantly from the internal sphincter, and the outer balloon recording from the bulk of the external sphincter. This technique affords only a partial separation of the actions of the voluntary and involuntary muscles of the anal sphincter.

We have developed a combined multiport manometric and electromyographic technique, which allows us to separate and identify the individual actions of the internal and external sphincters. In this study, the technique has been used to describe the action of the two muscles during rectal distension in normal volunteers and to characterize the abnormalities found in patients with idiopathic faecal incontinence.

Patients and methods

Subjects

The normal group consisted of 11 women (five nulliparous, three multiparous, i.e. more than three children) who were aged between 20 and 51 years (median 36 years) and were either healthy hospital workers or patients admitted for treatment of surgical conditions not involving the gastrointestinal tract. The incontinent patients were 18 women (one nulliparous, eight multiparous) aged between 28 and 75 years (median 59 years). Episodes of incontinence occurred at least once a day in 11 patients and between once a day and once a month in the remainder. Seven patients were incontinent to both solids and liquids, the rest were only incontinent when their motions were liquid. Clinical examination revealed no evidence of generalized neuropathy or myopathy or previous sphincter trauma, though all of the patients had abnormal descent of the pelvic floor (more than 2 cm) on straining.

Methods

Pressures were measured at six sites in the anal canal, during serial inflation of a rectal balloon with increasing volumes of air[5]. The probe was a polyvinyl seven-lumen tube, external diameter 5 mm (Mui, Missisauga, Ontario, Canada). Six of the channels terminated in side holes situated 0·5, 1·0, 1·5, 2·0, 2·5 and 3·5 cm from the anal margin and were perfused with water, at a rate of 1 ml/min, using a low compliance

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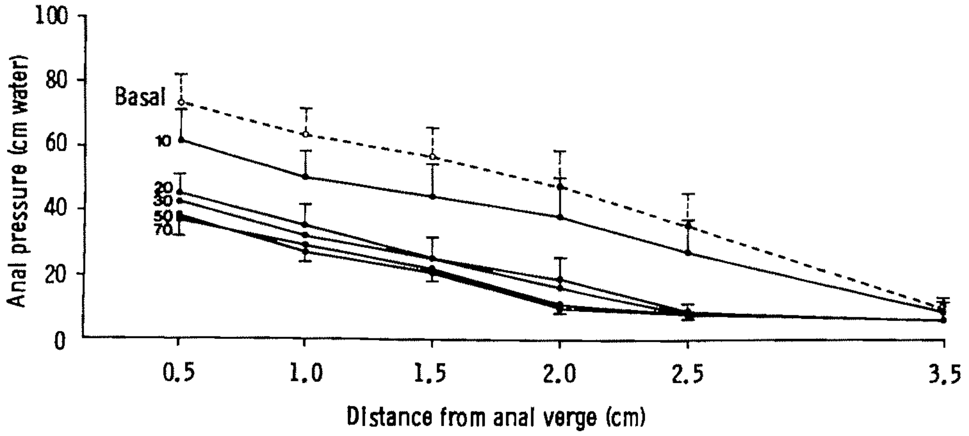

Figure 1 *The anal pressure profile at rest and during distension of a rectal balloon with 10, 20, 30, 50 and 70 ml of air. Results are the means (s e m) of data from 11 control subjects*

reservoir and capillary tubing (Mui) Intraluminal pressure was measured by means of water-filled transducers (Statham 230B, Oxnard, California, USA) situated in each infusion line, and the output of each transducer was recorded on an eight-channel recorder (Hewlett Packard 7758A, Waltham, Massachusetts, USA) The seventh channel terminated in a small latex balloon, manufactured from the teat of a rubber condom (LRC Products Ltd, London), located so that its lower pole was 7 0 cm from the anal margin

The electrical activity of the external sphincter was assessed in six control subjects and 15 incontinent patients by means of a bipolar electrode, consisting of two Trimel (Johnson Mathey Metals Ltd , Southgate, London, UK) coated wires (diameter 0 025 mm) with the ends bared, hooked and offset to avoid electrical contact[6] The wires were inserted into the superficial part of the sphincter[7] using a fine gauge hypodermic needle, which was subsequently withdrawn, leaving the hooked wires *in situ*. The free ends of the wires were bared and attached to an amplifier (Type 14A 11 electromyograph, DISA, Copenhagen, Denmark), which was connected via an integrator to the chart recorder.

With the subject lying in the left lateral position, the probe was positioned in the anorectum using a proctoscope, and the electomyograph wires were inserted into the external sphincter Both the probe and the wires were taped to the buttocks to prevent movement during the test Fifteen minutes were allowed for the anal canal to adapt to the presence of the tube The rectum was distended by inflating the terminal balloon with 10 ml of air Distension was maintained for 60 s. The balloon was then deflated and, after a recovery period of at least 60 s, it was reinflated at a rate of approximately 20 ml/s, with the previous volume plus 10 ml This procedure was continued to a balloon volume of 100 ml.

In addition, maximum basal and maximum squeeze anal pressures were measured, in all patients and controls, by the station pull-through technique[8]

Statistical analysis

Statistical analysis was performed using the Student's *t* test and Wilcoxon's rank sum test for parametric and non-parametric data respectively.

Results

Normal subjects

The resting pressures in the anal canal described an asymmetric profile with the greatest pressures recorded caudally (*Figure 1*). The maximum resting pressure was defined as the highest pressure recorded at any point in the anal canal, after the pressure had stabilized to steady levels.

Distension of the rectum caused an initial increase in anal pressure, most obvious in the more caudad channels and accompanied by an increase in the electrical activity of the external sphincter (*Figure 2*). The maximum contractile response was defined as the maximum increase in pressure induced, at any site in the anal canal, at any volume of rectal distension. This response was followed by a reduction in pressure, throughout the anal canal, to values that were below the resting levels (*Figure 2*) The reduction in anal pressure was not associated with any decrease in the electrical activity of the external sphincter. In most cases the sphincter activity remained elevated above the resting levels throughout the period of distension (*Figure 2*). The depth of relaxation increased with distending volumes up to 50 ml and the highest pressure recorded in any of the anal channels during anal relaxation, induced by rectal distension with volumes exceeding 50 ml, was termed the maximum residual pressure If we can assume that the internal sphincter was maximally inhibited by volumes of 50 ml and above, the maximum residual pressure reflected the residual activity of the external sphincter.

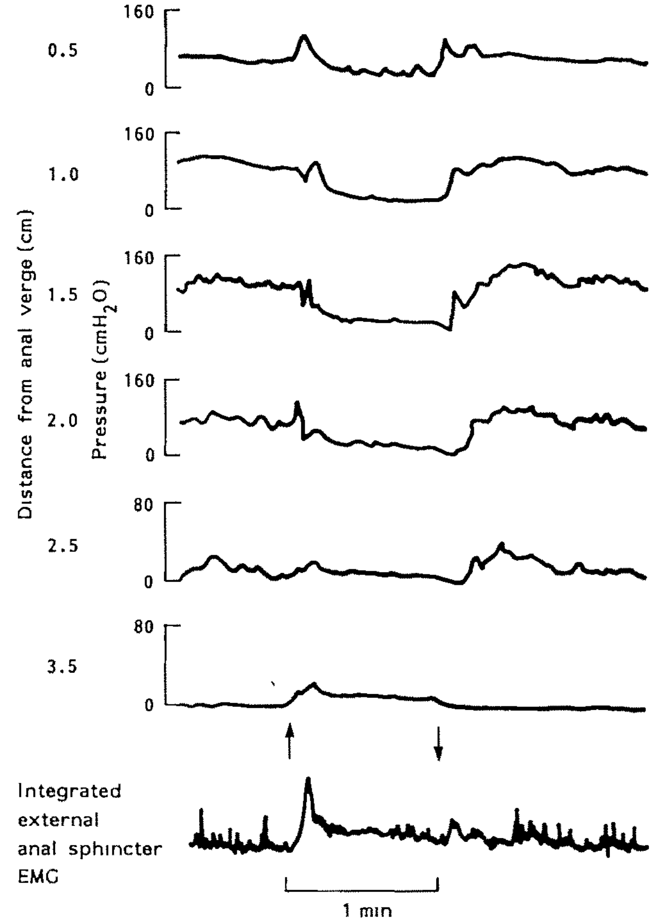

Figure 2 *Multiport recording of anorectal pressure (cmH$_2$O) and external anal sphincter electrical activity in a normal female subject during inflation of a 50-ml balloon for 1 min ↑, Inflation, ↓, deflation, EMG, electromyograph*

Table 1 *Anal pressures during station pull-through and during rectal distension*

	Normal controls ($n=11$)	Incontinent patients Group 1 ($n=12$)	Incontinent patients Group 2 ($n=6$)
Station pull-through			
Mean highest basal pressure	96 (6)	53 (6)*	38 (4)*†
Mean highest squeeze pressure	200 (18)	107 (15)*	98 (17)*
Six-channel probe			
Maximum resting pressure	75 (7)	53 (7)*	22 (3)*†
Maximum residual pressure	41 (4)	22 (5)*	17 (1)*
Maximum pressure recorded during rectal distension	109 (13)	79 (13)*	59 (9)*†
Maximum reduction in pressure recorded during rectal distension	52 (7)	48 (11)	2 (1)*†
Maximum contractile response	41 (12)	40 (14)	41 (8)

Results expressed as mean (s e m.) pressures (cmH_2O). *$P<0{\cdot}05$ compared with control group, †$P<0{\cdot}05$ compared with group 1 (Wilcoxon's rank sum test)

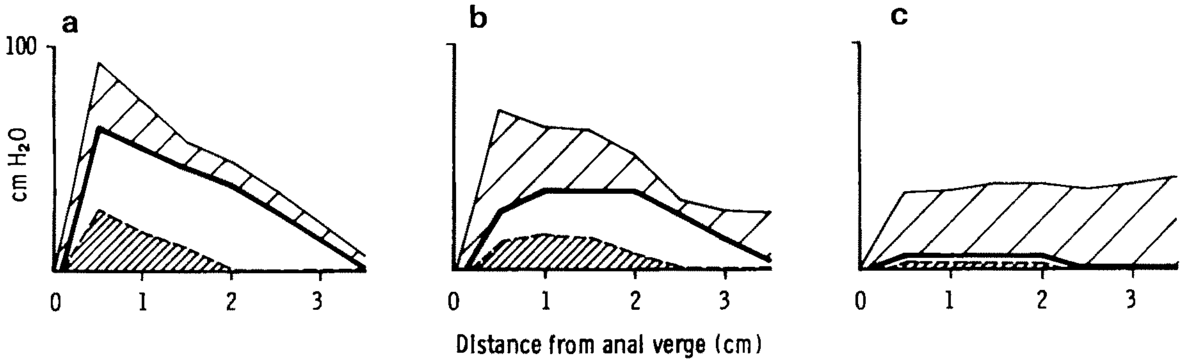

Figure 3 *Average profiles of resting pressure (———), residual pressure (----) and maximum pressure recorded during the inflation reflex (—) in* **a** *normal subjects,* **b** *group 1 incontinent patients with normal anal relaxation and* **c** *group 2 incontinent patients with no anal relaxation*

The depth of relaxation observed with each rectal volume was virtually identical at each recording site up to 2·0 cm from the anal margin (*Figure 1*). The innermost recording site, situated 3·5 cm from the anal margin, was almost certainly in the rectum, as the pressures in this channel were always very low and no relaxation was observed on rectal distension. If that is correct, the ports, situated 2·5 and 2·0 cm from the anal verge, recorded rectal pressure when the rectum was distended with volumes of 20 or 50 ml, respectively (*Figure 1*). Thus, because of the asymmetry of the anal pressure profile, lower volumes were required to produce a maximum inhibition of the inner anal ports than of the outer anal ports, and the sphincter appeared to shorten as the rectum was distended (*Figure 1*).

At small distending volumes, the sphincter showed only transient relaxations, the pressure returning to basal values whilst the balloon was still inflated. As the distending volume increased, the sphincter tone remained below the resting levels for the duration of the distension, but rose rapidly to levels that often exceeded the resting pressures when the balloon was deflated (*Figure 2*). This 'rebound' rise in pressure was usually, but not invariably, accompanied by a transient increase in the electrical activity of the sphincter (*Figure 2*), which was always shorter.

Incontinent subjects

The incontinent patients showed two patterns of anal response to rectal distension. Twelve patients (group 1) aged 28–75 years (median 49 years) showed normal anal relaxation, but the contractile responses were absent in two cases and maximum resting pressures, maximum pressures recorded during the 'inflation reflex' and maximum residual pressures were all lower than in the controls (*Table 1, Figure 3*). The pressure profiles differed from the control subjects in that the maximum resting and residual pressures were recorded between 1 and 2 cm from the anal margin and not in the outermost channels (*Figure 3*). The maximum reduction in anal pressures recorded during rectal distension was not significantly different from that observed in the normal controls (*Table 1*) although, unlike normal subjects, the relaxation was asymmetrical, being maximal in the inner channels.

The remaining six patients (group 2), aged 52–75 years (median 65 years), showed no anal relaxation in response to rectal distension (*Figure 4*). The maximum resting pressures in these patients were lower than in the control group and group 1 patients ($P<0{\cdot}05$; *Table 1, Figure 3*). The contractile responses to rectal distension were similar in amplitude to those of the normal controls (*Table 1*), although the maximum anal pressures, recorded during a contractile response, were lower than in the normal group or group 1 incontinent patients ($P<0{\cdot}05$; *Table 1, Figure 3*). The steady-state pressures recorded during rectal distension (corresponding to the residual pressure in the other groups) were lower than in the controls (*Table 1*).

During station pull-through, the maximum basal and the maximum squeeze pressures were significantly lower in both groups of incontinent patients compared with control subjects, and the maximal basal pressures in group 2 incontinent patients were lower than those in group 1 patients (*Table 1*).

Patients in group 2 tended to suffer more severe symptoms than those in group 1; five out of six patients in group 2 but only two out of twelve patients in group 1 ($P<0{\cdot}05$; Fisher's exact test) were incontinent of solids as well as liquids

Discussion

The results show that the normal anal sphincter is asymmetric; the resting pressure is not uniform along its length, but is higher caudally. The asymmetry can be explained by the tonic contraction of the external sphincter, the bulk of which is situated around the outer anal canal. The initial brief increase in pressure, induced by rectal distension, is associated with an

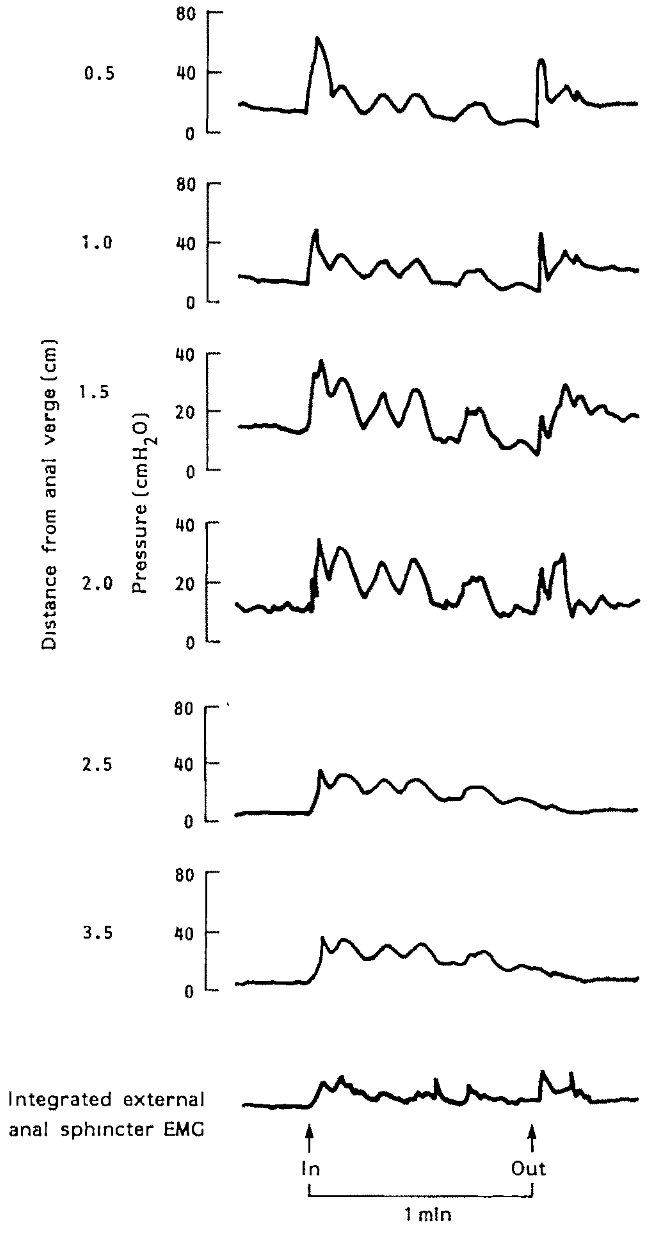

Figure 4 *Multiport recording of anorectal pressure and the electrical activity of the external anal sphincter in a patient with idiopathic faecal incontinence (group 2) during inflation of a rectal balloon with 50 ml of air. In, inflation, out, deflation, EMG, electromyograph*

increase in sphincter electrical activity and accentuates the anal pressure gradient. The ensuing reduction in anal pressure, which is caused by relaxation of the internal sphincter, induces a similar degree of relaxation in pressure throughout the anal canal, indicating that the sphincter is functionally homogeneous along the length of the anal canal in normal subjects

Increasing the volume of distension up to 50 ml increases the depth and the duration of relaxation. This causes the pressure in the upper anal canal, 2·0 and 2·5 cm from the anal margin, to fall to values that are equal to those recorded in the innermost port (3·5 cm from the anal margin), which is assumed to be situated in the rectum Thus, the anal sphincter shortens during rectal distension due to relaxation of the internal sphincter, while the concomitant contraction of the external sphincter maintains continence by keeping the outer anal canal tightly closed. The impression, gained from these manometric studies, corresponds to the radiological appearances during distension of the rectum with barium[9]. Thus, as has been previously suggested, relaxation of the internal sphincter could allow the rectal contents to be sampled by receptors in the upper anal canal[10], while continence is preserved by contraction of the external sphincter.

Comparison of the residual with the resting pressures suggests that the external sphincter could provide up to 50 per cent of the resting tone of the sphincter in normal subjects. This value is considerably higher than previously published data[11,12], and may be explained by the fact that rectal distension can cause a prolonged stimulation of external sphincter activity (*Figure 2*), and therefore residual pressure probably provides an overestimate of resting tone.

It is often assumed that the puborectalis contracts at the same time as the external sphincter but, if this is so, it does not increase the pressure in the inner anal canal. This is hardly surprising, as contraction of a muscle that loops around the posterior aspect of the inner anal canal will move the inner anus forward and accentuate the anorectal angle, but will not increase the intraluminal pressure unless movement of the upper anus is prevented by a relatively fixed object such as the prostate gland in the male or perhaps the cervix uteri in the female.

Deflation of the rectal balloon is often accompanied by a brief increase in sphincter pressure, which is related to a correspondingly transient increase in the electrical activity of the external sphincter, and a more sustained increase in sphincter tone, which is presumably caused by increased activity in the internal sphincter, as external sphincter activity rapidly returns to resting levels after balloon deflation

Studies carried out in incontinent patients revealed two distinct manometric patterns in response to balloon distension Most patients (group 1) showed a normal pattern of relaxation. The resting and residual pressure profiles in these patients differed from those in normal subjects in that the maximum pressure was recorded at the midpoint of the anal canal instead of at the caudad pole, suggesting a relative weakness of the external sphincter. This conclusion was supported by the relatively low squeeze pressure, measured by the station pull-through technique, and by the low maximum residual pressures in this group. The maximum decreases in anal pressure, induced by rectal distension, were similar in amplitude in this group to those observed in the control group, implying normal internal sphincter tone, though the asymmetric profile of relaxation may suggest impaired tonic contraction of the internal sphincter in the outermost anal channels.

The remainder of the incontinent patients showed no anal relaxation in response to rectal distension Their very low basal pressures excluded the possibility that they had Hirschsprung's disease[13–15]. Instead, the results suggest that the internal sphincter is abnormally weak and making little, if any, contribution to the anal sphincter pressure. Rectal distension in these patients increased the pressure in the anal canal in a pattern that resembled the profile of the integrated electrical activity of the external sphincter. These observations resemble the pattern, previously observed during continuous rectal infusion of saline, when 59 per cent of a group of patients with severe faecal incontinence showed no anal relaxations, but showed instead regular increases in pressure throughout the anorectum[16]. The external sphincter pressure and electrical responses to rectal distension in group 2 patients were similar in amplitude to the corresponding responses recorded in control subjects, although the maximum squeeze pressure was not only lower than in the normal controls, but also lower than in group 1 patients. The maximum residual pressure, a measure of external sphincter tonic activity, was also lower in group 2 than in controls. Thus, it would appear that in group 2 patients internal, as well as external, sphincter function is impaired This could explain why more group 2 patients were incontinent to solids as well as liquids. The older age of the group 2 patients would be consistent with a progression from a situation dominated by external sphincter weakness into one in which the internal sphincter is also impaired.

Internal sphincter weakness has been suggested to be partially responsible for the faecal incontinence seen in diabetic patients with autonomic neuropathy[17]. None of our patients had diabetes mellitus or any other signs of autonomic nerve dysfunction. However, all of them had external sphincter impairment and abnormal descent of the pelvic floor. Perhaps the internal sphincter normally requires some structural support to maintain normal tone. If so, exposure to traction from the unsupported tissues of the pelvic floor could result in stretching of the sphincter and apparent weakness. Another possible mechanism may involve stretch damage to the arteries or the fragile autonomic nerves that supply the sphincter.

The role of the internal sphincter in the pathophysiology of faecal incontinence is controversial. An abnormally weak sphincter would presumably allow the liquid faeces direct access to the anal canal. This may mean not only that the external sphincter would have insufficient time to respond to the entry of faeces into the rectum but also that it may become densensitized by continuous exposure to rectal contents. Another important factor is that there seems to be a reciprocal relationship between the contractile activities of the external and internal sphincters; when the internal sphincter is relaxed during rectal distension, the external sphincter contracts to maintain continence; when the external sphincter is relaxed during micturition it is the tone in the internal sphincter that preserves continence[18]. Thus, it seems logical that impairment of both muscles should lead to more severe incontinence than impairment of one muscle alone.

The tone of the internal sphincter, unlike the external sphincter, can be influenced by pharmacological agents. Loperamide has been shown to increase resting sphincter pressure and to modulate the internal sphincter response to rectal distension[19]. α-Adrenoreceptor agonists enhance internal sphincter tone *in vitro*[20,21] and *in vivo*[22] and have been used to treat urinary incontinence. The use of such agents in patients with idiopathic incontinence and demonstrable internal sphincter weakness may prove a useful adjunct to alternative modes of treatment.

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Surgical Research Society

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The 69th Meeting of the Surgical Research Society took place on 5 and 6 Janury 1989 at the University of Kent, Canterbury. The Meeting was organized by Professor Williams and the staff of the Department of Surgery at The London Hospital, and Professor G. R. Giles was in the Chair. A Symposium entitled 'Gastrointestinal motility for the surgeon' preceded the free paper sessions. One hundred and four papers were read, and the Patey Prize was awarded to Mr M. G. Dunlop, for his presentation entitled 'Familial adenomatous polyposis (FAP): gene order at the FAP gene locus with evidence to support the hypothesis that the germ line mutation is sufficient for the development of colonic adenomata'. A selection of papers and abstracts is published on pp. 622–649.

Rehabilitation after lower limb amputation: a comparative study of above-knee, through-knee and Gritti–Stokes amputations

A. Houghton, A. Allen, R. Luff and I. McColl

Department of Surgery, Guy's Hospital, London SE1, UK
Correspondence to:
Professor I. McColl

A study of 169 unilateral amputees under three Disablement Services Centres was performed. The study comprised 88 above-knee, 54 through-knee and 27 Gritti–Stokes amputations. Satisfactory rehabilitation occurred in 33 per cent of above-knee, 62 per cent of through-knee and 44 per cent of Gritti–Stokes patients (56 per cent overall). The better rehabilitation of through-knee versus *above-knee amputees* ($P<0\cdot02$) *was also found in a group of patients matched for comparable age and duration of amputation as well as in a group of age-matched vascular amputees. Through-knee amputees relied significantly less on wheelchairs than above-knee* ($P=0\cdot016$) *and Gritti–Stokes* ($P=0\cdot05$) *amputees. The prosthesis used for the through-knee and Gritti–Stokes amputations was considered unsightly in 50 per cent of cases* (versus *31 per cent for the above-knee prosthesis).*

The superior rehabilitation with through-knee amputations should prompt us to improve both our technique for this amputation and the prostheses currently available. A through-knee amputation should be performed in preference to an above-knee amputation in the case where either is surgically possible, and a below-knee amputation not feasible.

Keywords: Amputation, rehabilitation, lower limb

In 1986 there were 5596 new referrals for artificial limbs in England, Wales and Northern Ireland[1] These were mainly for lower limb amputations A below-knee amputation is preferred where possible[2–4], but may fail to heal in up to 30 per cent of cases, resulting in a higher amputation[4–6].

When a more proximal amputation is needed there is controversy over the place of the Gritti–Stokes, through-knee and above-knee amputations. Proponents of the Gritti–Stokes amputation point to the superior primary healing (75–90 per cent of cases), rapid postoperative mobility owing to the long lever, and low perioperative mortality rate of around 10 per cent[7–9]. Like the Gritti–Stokes amputation, the through-knee amputation has a perioperative mortality rate of 10 per cent, but has been suggested to have a lower primary healing rate[3,10]. The broad, strong bulbous stump does, however, provide total end-bearing and there is no need for a pelvic band to prevent rotation. A standard above-knee amputation is associated with a higher perioperative mortality rate of 20 per cent[7,10,11], but has the advantage that the prosthesis is cosmetically superior and weighs less than a comparable through-knee or Gritti–Stokes prosthesis.

There is, however, little in the literature comparing rehabilitation following these three amputations Many surgeons aim to preserve the maximum amount of the patient's own limb on the assumption that any extra limb length must be beneficial. Others have been convinced of the prosthetic advantages of the above-knee stump and have adopted a policy of performing an above-knee amputation whenever a below-knee amputation is not possible[12]

This study was designed to assess patients with these three lower limb amputations, looking specifically at their rehabilitation from the time of first attendence for prosthetic treatment. It was therefore a study of potential limb-wearers and was designed to help answer the question: 'If a below-knee amputation is impossible, which amputation offers the patient the best chance of successful rehabilitation'

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Table 1 *The questions asked of each patient to assess rehabilitation*

		Score
1. Did patients use their limb to walk during		
a less than 25 per cent of waking hours		0
b between 25 per cent and 50 per cent of waking hours		1
c. more than 50 per cent of waking hours		2
d all their waking hours		3
2 Did patients use their limb to walk·		
a just when visting the doctor or limb-fitting centre		0
b at home but not to go outside		1
c. outside the home on occasions		2
d inside and outside all the time		3
3 When going outside wearing their limb did patients:		
a. use a wheelchair		0
b use two crutches, two sticks or a walking frame		1
c use 1 stick		2
d. use nothing		3
4. When walking with their limb outside did patients feel unstable when.		
a walking on the flat	No	1
b. walking on slopes	No	1
c walking on rough ground	No	1
Yes to any section		0
If they used a wheelchair outside they scored 0 for question 4		

The maximum score = 12

Table 2 *Details of the 169 unilateral amputees studied*

	Above-knee	Through-knee	Gritti–Stokes
Number	91	54	27
Mean age in years (range)	65 (23–93)	61 (27–87)	64 (22–91)
Mean number of years after amputation (range)	24 (1–71)	14 (1–64)	9 (1–71)

Patients and methods

The names and addresses of 250 patients with above-knee, through-knee and Gritti–Stokes amputations were obtained from the Disablement Services Centres of Roehampton, Gillingham and Brighton We eliminated from this study bilateral amputees, congenital limb deficiency and amputees under the age of 20, leaving 229 patients The date of amputation and its level was determined from the notes Questionnaires were then sent to each patient. Rehabilitation was assessed by the answers to four questions (*Table 1*) A score of nine or more was accepted as satisfactory rehabilitation The patients were also asked whether they had a wheelchair and for how many of their waking hours they used it. The answers to these questions were analysed to assess the patients' wheelchair dependence.

The reasons for patients not wearing their prosthesis were assessed Was this due to tenderness of the stump, blisters or ulcers, the limb being generally uncomfortable or cosmetically unattractive? In a separate question the patients' views were sought about the cosmesis of the artificial limb Statistical difference between the groups was assessed using the Mann–Whitney U test

Results

Questionnaires were sent to 229 amputees and the response rate was 74 per cent. Useful replies were received from 169 patients (132 male and 37 female). These replies are shown in *Table 2*

There was no difference in the mean age of the different amputation groups. However, above-knee amputees had had their amputation a mean of 24 years previously compared with 14 years for through-knee amputees and 9 years for Gritti–Stokes amputees. Above-knee amputees were therefore younger on average when prosthetic treatment started.

In view of these differences we selected a group of responders for comparable age and duration of amputation. This group included 16 Gritti–Stokes, 21 through-knee and 23 above-knee amputees.

Of the 169 replies, eight patients (4·7 per cent) had no functional use of their limb (*Table 3*)

The cause of the amputation could be determined from the notes in 78 per cent. Trauma was responsible in 48 per cent and vascular disease in 34 per cent Other causes, including bone tumours, polio and developed non-union accounted for the remaining 17 per cent. Aetiological proportions were similar to these figures for above-knee and through-knee amputees but the Gritti–Stokes amputations were predominantly performed for vascular disease (69 per cent). In the age/duration-matched group, vascular disease was the cause in 61 per cent of above-knee, 38 per cent of through-knee and 71 per cent of Gritti–Stokes amputees. Trauma was responsible in 28 per cent, 54 per cent and 21 per cent, respectively.

A group of vascular amputees was age-matched to ensure that differences in outcome would not merely be a reflection of the cause of amputation. This group included 18 above-knee, 14 Gritti–Stokes and eight through-knee amputees.

Rehabilitation

Fifty-six per cent of patients were satisfactorily rehabilitated as defined by a score of nine or more on the four questions in *Table 1*. This group comprised 47 of 86 above-knee (54 per cent), 34 of 50 through-knee (68 per cent), and 13 of 25 Gritti–Stokes amputees (52 per cent). In the age/duration-matched group, 33 per cent of the above-knee, 62 per cent of the through-knee and 44 per cent of the Gritti–Stokes patients underwent successful rehabilitation. On statistical analysis the through-knee amputees rehabilitated better than the above-knee amputees ($P<0\cdot02$) in both non-matched and matched groups, and better also than the Gritti–Stokes amputees, although this fell short of statistical significance ($P=0\cdot08$). The better rehabilitation of the through-knee amputees was maintained in the group of age-matched vascular amputees. In this group the mean rehabilitation scores were 6·9, 7·1 and 8·3 for above-knee, Gritti–Stokes and through-knee amputees, respectively ($P<0\cdot07$ through-knee *versus* above-knee).

When we looked at the question on stability in isolation, 74 per cent of all above-knee amputees reported being unstable on slopes compared with 28 per cent of through-knee and 56 per cent of Gritti–Stokes. There was less difference on rough ground where 79 per cent above-knee, 65 per cent through-knee and 67 per cent Gritti–Stokes felt unstable.

Wheelchair use

Seventy-nine per cent of our patients never used a wheelchair—86 per cent of above-knee, 68 per cent of Gritti–Stokes and 88 per cent of through-knee amputees. Five patients in each group stayed in a wheelchair all the time. When going outside, seven of the Gritti–Stokes, 11 of the above-knee, and three of the through-knee amputees used a wheelchair. In the age/duration-matched group, both above-knee and Gritti–Stokes amputees were significantly more reliant on their wheelchairs than through-knee patients ($P=0\cdot016$ for above-knee *versus* through-knee, $P=0\cdot05$ for Gritti–Stokes *versus* through-knee). In the age-matched vascular amputees, above-knee amputees

Table 3 *Details of patients without functional use of their limb*

Amputation type	Age	Reasons for not using limb
Through-knee	84	Very heavy and cumbersome
Through-knee	86	Both hips in fixed flexion
Through-knee	72	Other limb deteriorating
Through-knee	83	Recent stroke
Above-knee	90	Ulcer on stump
Above-knee	77	Painful stump
Gritti–Stokes	76	Unable to fit limb (arthritic)
Gritti–Stokes	86	Unable to fit limb

were more reliant on their chairs than through-knee amputees ($P < 0{\cdot}05$). There was little difference between the Gritti–Stokes and the above-knee amputees in any group.

Cosmesis

Our results confirmed some previous reports. The prosthesis used for the through-knee and Gritti–Stokes amputation is essentially the same and was felt to be unattractive in a greater number of cases than the above-knee prosthesis (50 *versus* 31 per cent). As expected, this was a greater problem in women, 75 per cent of whom found the prosthesis unattractive compared with 50 per cent of men

There was no difference between the three groups in terms of local stump problems or the reported frequency of artificial limb repair.

Discussion

The overall number of patients satisfactorily rehabilitated to our rehabilitation score of nine is good (56 per cent). The very high proportion of patients who never use a wheelchair emphasizes that this study is predominantly one of current limb-wearers. The high prevalence of traumatic amputees in this study (48 per cent) is perhaps a reflection of this. The normal incidence of traumatic amputation is 7·9 per cent[13].

We have shown that through-knee amputees rehabilitate better and rely on wheelchairs less than above-knee and Gritti–Stokes amputees. This is in agreement with the results of another recent study[14]. The through-knee amputee is more stable, especially when walking up or down slopes; presumably this is due at least in part to the wide bulbous end-bearing stump of this amputation which is associated with retention of proprioception and greater durability[15] These features of the stump also enable early postoperative mobilization on a pneumatic postamputation mobility aid.

It might be thought that rehabilitation differences could be explained by above-knee amputees being less fit. In this study there were a larger number of vascular patients in the above-knee than in the through-knee group The trend to better rehabilitation of the through-knee amputee in the group of age-matched vascular patients was, however, still present. Moreover, Green *et al* [11], in their study of above-knee and through-knee amputees, found through-knee amputees to be no fitter.

It is noteworthy in our study that above-knee amputees were on average younger at the time of amputation and would therefore be expected to rehabilitate better No trend in this direction is present.

The Gritti–Stokes amputees in this study were more reliant on wheelchairs than the through-knee amputees, an important finding in view of the similar stump length It may reflect lack of stability, either due to a mobile patella or the narrow conical shape of the stump enabling easy rotation of the prosthesis. It should, however, be emphasized that this series included only 27 Gritti–Stokes amputations performed by several different surgeons It would be helpful to do a comparable study on the rehabilitation of a greater number of patients in a centre where this amputation is done frequently. We must also stress that the Gritti–Stokes amputation, with its excellent record for primary healing, is a good amputation for patients not being considered for artificial limbs One problem, concerning both the through-knee and Gritti–Stokes amputation, highlighted in this study is that the prosthesis is unattractive. This is more of a problem in women where the protruding knee may be more obvious and may also cause problems when travelling on public transport.

The through-knee amputation has fallen into disrepute on account of local complications[3,10,11] in the postoperative period. A recent study, however, found this not to be the case[14]. This study used anterior and posterior flaps, although it has been suggested that the utilization of flaps based medially and laterally may give the best results[15].

We do not have information on the perioperative complications in our series or indeed on the number of each amputation type requiring reamputation. Our results suggest that a greater failure and reamputation rate should be accepted with the through-knee amputation, just as with a below-knee amputation The superior rehabilitation with this form of amputation, as with a below-knee, should prompt us to improve both our technique for this amputation and the prostheses currently available.

In the UK in 1985, only 4 per cent of lower limb amputations were at the level of the knee[16]. Our study suggests that the place of the through-knee amputation should be re-examined. It has been shown to give significantly better patient rehabilitation when compared with both the above-knee and Gritti–Stokes amputation. When taking mortality statistics into account, it should be performed instead of an above-knee amputation in cases where either is surgically possible Further studies are needed to evaluate the Gritti–Stokes amputation but our study suggests that successful rehabilitation is less likely than with the through-knee amputation.

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Surgical Research Society Abstracts

Late perfusion, a simple remedy for renal allograft primary non-function?

N.R Parrott, J L.R. Forsythe, T.W.J. Lennard, K.M. Rigg, G Proud and R.M.R. Taylor, *Renal Transplant Unit, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, UK*

The renal transplant with primary non-function presents problems in terms of diagnosis of rejection, dialysis work-load, and duration of hospital stay It is suggested that primary non-function (PNF) is due to the calcium paradox and may be prevented by calcium antagonists The incidence of PNF has been examined in a series of 124 consecutive renal transplants The first 106 patients had *in situ* perfusion alone, and had a PNF rate of 57·5 per cent The second group of patients had identical *in situ* perfusion, but were reperfused immediately before implantation ('late perfusion'). In this group, the PNF rate was 27·8 per cent. The difference was highly significant, $\chi^2=4{\cdot}35$, $P=0{\cdot}035$. The two groups were well matched for age and sex, as well as for donor age, blood pressure and human leucocyte antigen matching. The recipients in the two groups were also well matched for age, blood pressure on clamp release, cold ischaemia, second warm and total ischaemic times, form of dialysis, and transplant number Using stepwise logistic regression, only three factors were significantly associated with PNF. late perfusion ($P=0{\cdot}003$), second warm ischaemia >35 min ($P=0{\cdot}002$), and immunosuppressive agent ($P=0{\cdot}01$). It is concluded that PNF can be alleviated by the simple expedient of 'late perfusion' without recourse to potentially harmful calcium channel blockers.

Apocrine differentiation: a new prognostic factor for breast cancer

N.J. Bundred, R.A Walker, G.K. White, H.J. Stewart and W.R. Miller, *Departments of Surgery and Pathology, University of Leicester and Department of Surgery, Royal Infirmary, Edinburgh, UK*

The importance of apocrine differentiation in breast carcinoma remains unknown An immunoperoxidase method to detect zinc α_2-glycoprotein, an apocrine marker[1], has been used to identify apocrine differentiation in human breast cancers objectively and determine if the expression of differentiation by tumours is of clinical significance.

Breast tumour samples tested from 145 women, with a minimum follow-up of 5 years, were assessed using routinely fixed and processed tissue

Sixty-six (45 per cent) tumours did not stain with the antibody, 52 (36 per cent) exhibited positive apocrine staining whilst 27 (19 per cent) were equivocal. The presence of apocrine differentiation was unrelated to lymph node status, menstrual status, tumour grade or size, oestrogen receptor (E_2R) or progesterone receptor status Patients whose tumours exhibited apocrine staining had a shorter disease free interval (DFI) ($P=0{\cdot}04$) and survival ($P=0{\cdot}05$).

A Cox's multiple regression analysis showed that the presence of staining added significantly to the value of node status ($P=0{\cdot}0002$), menstrual status ($P=0{\cdot}0006$), tumour size ($P=0{\cdot}0008$) and E_2R status ($P=0{\cdot}0004$) in the prediction of DFI and survival. The other seven prognostic factors tested were not statistically significant and were not included in the model.

Apocrine differentiation in breast cancer appears to be an independent predictor of poor-prognosis tumours.

1. Bundred NJ, Miller WR, Walker RA. An immunohistochemical study of the tissue distribution of the breast cyst fluid protein zinc α_2-glycoprotein. *Histopathology* 1987; 11. 603–10.

Ileal adaptation following restorative proctocolectomy

W.A. Kmiot, D.J. Youngs, M.C. Winslet, F.T. Curran and M R.B. Keighley, *The General Hospital, Birmingham, UK*

Following restorative proctocolectomy, pouch ileal mucosa undergoes villous atrophy and crypt hyperplasia. To identify concurrent adaptive change in ileal mucosal cell kinetics, we have measured the crypt-cell production rate (CCPR) using a stathmokinetic technique in 15 patients before and 6 months after pouch formation These values were correlated with morphometric estimates of villous height and crypt depth A further CCPR estimate was obtained in the 7 of the 15 patients who had had their pouch defunctioned Validation studies established an organ culture time of 15 h and vincristine dose for metaphase arrest of 4 μg/ml. Linearity of metaphase accumulation was demonstrated for 3 h. Use of three time-points in normal ($n=50$) and pouch ileum ($n=45$) was validated by demonstrating 95 per cent confidence intervals of ±8 per cent and ±10 per cent of the respective means.

The CCPR was significantly higher in pouch ileum, showing a mean (standard error) of 2·49 (0·287) compared with normal ileum 1·35 (0·19), $t=6{\cdot}72$, $P<0{\cdot}01$ There was a decrease in CCPR when the pouch was constructed and defunctioned, with a median (range) of 1·35 (0·5–3·0) *versus* 0·9 (0·5–2·5), $z=2{\cdot}37$, $P<0{\cdot}02$, and a subsequent increase on restoration of intestinal continuity, 0·9 (0·5–2·5) *versus* 2·5 (1·4–4·4), $z=2{\cdot}04$, $P<0{\cdot}05$. An inverse relationship was demonstrated between CCPR and villous height ($r=-0{\cdot}92$, $P<0{\cdot}01$) and a direct relationship with crypt depth ($r=0{\cdot}83$, $P<0{\cdot}05$).

These data demonstrate increased CCPR in pouch ileum and the positively trophic effect of the faecal stream on ileal adaptation

Familial adenomatous polyposis (FAP): gene order at the FAP gene locus with evidence to support the hypothesis that the germ line mutation is sufficient for the development of colonic adenomas

M.G. Dunlop (introduced by A.N Smith), *Medical Research Council Human Genetics Unit, Western General Hospital, Edinburgh, UK*

Genetic linkage for familial adenomatous polyposis (FAP) has recently been established with probes C11P11 (Reference 1) and pi227 (Reference 2), mapping to chromosome 5q21–22 Gene ordering has not yet been possible but has important clinical and scientific implications Linkage analysis of six FAP families, including 111 genotyped and phenotyped individuals, is reported. Two C11P11–FAP and two pi227–FAP obligate recombinants were identified. One was recombinant for both, locating C11P11 and pi227 on the same side of the FAP locus. A further probable C11P11–FAP and pi227–FAP recombinant was detected Lod scores were calculated[3] to estimate genetic distances for each probe (peak Lod score for C11P11 of 5·57 at recombination fraction 0·07; and for pi227, 3·49 at 0·11), placing C11P11 closest to FAP. Gene order is therefore pi227–C11P11–FAP

Having identified C11P11 as the closest marker to FAP, the hypothesis that the germ line mutation is sufficient for the development of colonic adenomas[1,4] was tested by a search for gene loss No loss for C11P11 constitutional heterozygosity was found in 19 adenomas from three FAP patients, suggesting preservation of the FAP gene on the normal chromosome 5. Therefore it appears that haploid insufficiency of the FAP gene allows adenomatous change in the colonic epithelium

1. Bodmer WF, Bailey CJ, Bodmer J *et al*. Localisation of the gene for familial adenomatous polyposis on chromosome 5 *Nature* 1987, **328** 614–6
2. Meera Khan P, Tops CMJ, Brock MCD *et al* Close linkage of a highly polymorphic marker (D5 S37) to familial adenomatous polyposis (FAP) and confirmation of FAP localisation on chromosome 5q21–22 *Hum Genet* 1988; **79**: 183–5.
3. Lathrop GM, Lalouel JM, Julier C, Ott J. Multilocus linkage analysis in humans detection of linkage and estimation of recombination *Am J Hum Genet* 1985, **37** 482–98.
4 Knudson AG. Hereditary cancer, oncogenes and antioncogenes. *Cancer Res* 1985, **45** 1437–43

Flow cytometric analysis of ductal carcinoma-in-situ (DCIS) of the breast

A.P. Locker, C.S. Dowle, C. Horrocks, A.S. Gilmour, I O. Ellis, C.W. Elston and R.W. Blamey, *Nottingham City Hospital, Nottingham, UK*

With the introduction of screening for breast cancer, DCIS has become a more common management problem The clinical behaviour of DCIS depends on histological type. Tumour DNA content relates to histological grade and clinical course in invasive breast cancer[1]

Of 74 patients with DCIS (follow-up from 18 to 144 months), eight have developed local recurrence. These were from 55 solid or mixed DCIS type; none of 15 cribriform tumours have recurred

Flow cytometry was used on paraffin-embedded tumours DNA indices and S-phase content were derived from these histograms

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Tumours were graded histologically according to mitotic index and pleomorphism The median S-phase was 3 per cent for the cribriform cancers and 11 per cent for the solid and mixed DCIS.

Table 1

Tumour type	Diploid/near diploid	Aneuploid
Cribriform	13	2
Mixed	8	15
Solid (including Comedo)	16	16
Papillary	1	3

$\chi^2=11{\cdot}15$ (3 d f.); $P<0{\cdot}02$

Table 2

	Histological grade		
Tumour type	1	2	3
Cribriform	14	1	0
Papillary	3	1	0
Mixed	9	10	4
Solid (including Comedo)	2	5	25

$\chi^2=67{\cdot}63$ (6 d f.); $P<0{\cdot}001$

These biological parameters considered together with our clinical observations suggest that cribriform DCIS is less aggressive than other types of DCIS, with important implications as to its management

1 Dowle CS, Owainati A, Robins A *et al.* Prognostic significance of the DNA content of human breast cancer. *Br J Surg* 1987, 74 133–6.

Is the multiple drug resistant gene (mdr-1) important in determining response to Adriamycin® in breast cancer?

S. Stallard, R. Brown, N. Keith, W.D George* and J.A. Bradley*, *Departments of Medical Oncology and *Surgery, Western Infirmary, Glasgow, UK*

Resistance to chemotherapy is a major cause of treatment failure in breast cancer Recent *in vitro* evidence suggests that one mechanism by which leukaemic and other cell lines develop drug resistance is the over-expression of a cell-membrane glycoprotein p180 encoded by the *mdr*-1 gene. In this study 30 freshly excised human primary breast cancers were examined to determine whether they expressed the *mdr*-1 gene and whether this related to their drug resistance to Adriamycin® (Farmitalia Carlo Erba, UK)

The mRNA was extracted from tumour tissue and *mdr*-1 gene expression was analysed by molecular hybridization to an *mdr*-1 probe. Quantitative analysis was performed by standardization of the results to a constantly expressed gene (β_2-microglobulin) and to total mRNA levels by hybridization to poly d (T). Chemoresponsiveness was measured by an *in vitro* colony-forming assay on tumour cells grown in short-term culture and expressed as the dose of Adriamycin causing 50 per cent inhibition of growth (ID_{50}).

All breast tumours were found to express the *mdr*-1 gene but the levels of gene expression varied widely (100-fold variation) between different tumours Glycoprotein p180 mRNA levels showed an inverse correlation with tumour sensitivity to Adriamycin ($r=-0{\cdot}71, P<0{\cdot}05$) These results support the hypothesis that the *mdr*-1 gene may play a role in determining the response of human breast cancer cells to chemotherapy.

Intraperitoneal production and systemic transfer of lymphokine-activated killer cells (LAKC) for treatment of disseminated gastrointestinal adenocarcinoma

D.H. Johnston, N.S. Williams, A.C Newland, M G. Macey, M. Turkish, P. O'Byrne, P. Durdey, J.Th. Bijman and G.R. Franks, *Departments of Surgery and Haematology, The London Hospital, London, UK*

Combined systemic therapy with recombinant interleukin 2 (rIL-2) and *in vitro* generated LAKC achieves responses for some advanced solid tumours, but toxic effects limit its use and treatment cost is prohibitive We have studied LAKC response after intraperitoneal infusion of lymphocytes from leukapheresed peripheral blood (LPBL) and rIL-2, and peritoneovenous transfer of LAKC by Denver ($n=5$) or Leveen ($n=1$) shunt. Incremental dosage of rIL-2 was administered by intraperitoneal infusion over 10 days ($11{\cdot}5$–$1{\cdot}35\times10^5$ units/kg per 24 h) Mild pyrexia ($n=6$), malaise ($n=6$), and anorexia and nausea ($n=3$) were observed. Abdominal discomfort ($n=2$) was controlled by non-opiate analgesia and five patients remained ambulant throughout treatment. Although lymphopenia and anaemia were evident, capillary leak syndrome did not occur Lymphocyte subset markers and natural killer activity to K562 targets (NKA) were studied serially by flow cytometric analyses.

Peritoneal	Day 1 mean (s e m)	Day 10 mean (s e m)	Paired *t* *n*
Helper:suppressor (CD4.8 ratio)	1·5 (0·4)	3·2 (0·6)	5 ($P<0{\cdot}01$)
IL-2 receptor + (CD25) proportion	1·9 (0·6)	21·6 (4·9)	5 ($P=0{\cdot}02$)
NKA (percentage killed)	8·8 (2·8)	47·7 (16·2)	4 ($P=0{\cdot}07$)
Peripheral blood NKA	8·7 (2·7)	25·3 (7·3)	3 ($P=0{\cdot}2$)

Repeated monthly treatments were possible ($n=4$, currently 2,2,3,7 cycles) Using this new technique a LAKC response can be induced within the peritoneal cavity and appears to be transferred into the systemic circulation It is cheap and well tolerated compared with systemic immunotherapy using *in vitro* generated LAKC, and may have the potential to revolutionize this type of treatment

Is there an increased risk of breast cancer in women who have a breast cyst aspirated?

N.J. Bundred, R R. West, J. O'Dowd and R.E. Mansel, *Departments of Surgery, Pathology and Community Medicine, University of Wales College of Medicine, Cardiff, UK*

Clinical studies suggest women who have breast cysts aspirated have an increased risk[1] of breast cancer but histologists claim only women with proliferative breast lesions are at risk[2]

A consecutive series of 644 women presenting with breast nodularity from 1976 to 1982 have been traced to determine their rate of subsequent breast cancer. 14 per cent had undergone breast biopsy. Five women had cancer diagnosed within a year of presentation and were excluded from further analysis The remaining 639 women fell into two groups, those with and those without a breast macrocyst which could be aspirated Ninety-one per cent of women have been followed up for 5 years or more (4129 women-years).

Age-specific person-years at risk were multiplied by national age-specific cancer registration rates (Office of Population Census Studies, 1983) to obtain an expected cancer incidence. Fifteen women have developed breast cancer, which is an excess risk in the macrocyst group of 5·8 times those with no macrocysts. Women with breast nodularity had no excess risk compared with expected incidence (see *Table*). Review of biopsy specimens revealed more epitheliosis in women with macrocysts ($P<0{\cdot}005$)

Macrocysts are clinical markers of histological proliferative breast lesions. Women who have had breast macrocysts aspirated have an increased risk of breast cancer and should be followed up.

		Cancers		
Diagnosis	*n*	Expected	Observed	Relative risk*
No macrocysts	287	1·1	1	1
Macrocysts aspirated	352	2·4	14	5·8

* Exact binomial test ($P<0{\cdot}001$)

1 Haagensen CD *Disease of the Breast*, 3rd ed Philadelphia Saunders, 1986. 250–66

2 Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease *N Engl J Med* 1985, 312 146–51

A new technique of colonic re-epithelialization by fenestrated ileal mucosal autografts

F C. Campbell and D.A. Hopwood, *Departments of Surgery and Pathology, Ninewells Hospital, Dundee, UK*

In short bowel syndrome (SBS) the colon is often normal, but absorbs little This study has devised and tested a method of expanding absorptive ileal mucosa into the colon

A fenestrated ileal mucosal graft is prepared from a 12-cm isolated loop, with intact vascular pedicle. The loop is denuded of muscle, fenestrated with opposing interdigitating incisions 1·5 cm apart, expanded to 20 cm, then grafted into a 20 cm loop of colon which has been stripped of its mucosa. Assessment of (1) graft 'take', (2) re-epithelialization time of fenestration, and (3) new mucosal architecture, was carried out in five test pigs. New mucosal function (4) was assessed by histological evaluation of fatty acid absorption, against normal ileum, of three control pigs

Successful graft 'take' occurred in all the four surviving test pigs. Re-epithelialization of all fenestrations (and the whole colonic loop) was complete in test animals by 5 weeks (healing time (s.d.)=3·8 (1·5) weeks). New mucosa was initially flat. At 8 weeks, villous architecture was restored but electron microscopy suggested persistent cellular immaturity. Fatty acid absorption by new grafted mucosa was indistinguishable from control ileal mucosa.

It was concluded that viable ileal mucosa can be harvested into colon, with a 66 per cent expansion of its surface area, with recovery of architecture and function. This method appears promising as a surgical approach to SBS.

A neosphincter for the treatment of faecal incontinence

N.S. Williams, R.I. Hallan, T. Koeze* and E.S. Watkins*, *Surgical Unit and *Neurosurgical Unit, The London Hospital, London, UK*

Patients with faecal incontinence in whom the conventional operations fail, or are contraindicated, may be treated by a gracilis sling procedure This operation is, however, rarely performed as the results are unpredictable. Chronic electrostimulation of the transposed gracilis has the theoretical advantage of converting the fast-twitch muscle to a slow-twitch muscle capable of fatigue resistance Such a property is vital if the muscle is to act as a sphincter.

Seven patients whose only alternative was a permanent stoma were treated by a gracilis sling procedure and implantation of a permanent electrostimulator (Medtronic) All patients had a covering stoma, and six were stimulated at 2–10 Hz continually for a minimum of 6 weeks. Manometry and a saline stress test were performed and fusion frequency was determined before and after stimulation (stim).

$n=5$	Without stim*	With stim	Paired t test
Maximum sphincter pressure (cmH$_2$O)	19·6±2·5	40·2±5·1	$P<0{\cdot}02$
Saline stress test· volume to leak (ml)	48·9±12·5	80·1±22·5	$P<0{\cdot}05$
	Pre-stim	After 6 weeks stim	
Fusion frequency (Hz)	24·6±0·4	17·3±1·2	$P<0{\cdot}001$

*Mean ± s.e.m.

These results indicate that electrical stimulation of the transposed gracilis muscle enhances its power to achieve continence. Furthermore chronic stimulation converts it to a slow-twitch muscle capable of contraction without fatigue This new technique should improve the results of the gracilis sling procedure but it remains to be seen how these patients will fare after their stomas are closed.

Is digital rectal examination a good guide to anal pressure?

A.W. Hall, M.J.G. Watkins, H.S. Hall and H.J. Pearson, *Departments of Surgery, University of Leicester and Department of Medical Physics and Clinical Engineering, Leicestershire Health Authority, Leicester, UK*

During assessment of patients with anorectal problems, anal tone is usually estimated on digital rectal examination As major treatment decisions are often made on this basis, the relationship of such empirical judgements to anal pressure is important

Fifty-three patients with various anorectal disorders were referred for detailed assessment. Immediately before the study each was examined by an experienced surgeon Anal tone was classified as poor/absent, normal or increased Whether the anus was closed or gaping was also noted. The anal pressure profile was determined using a 5 mm, balloon-ended catheter and a station pull-through technique. The maximum resting pressure was noted

Nineteen patients had poor or absent anal tone. Anal pressure in these varied from 14 to 132 cmH$_2$O (median 31). In 29 subjects assessed as 'normal' the range was 6·8–156 cmH$_2$O (median 82) and where tone was thought high, the range was 136–177 cmH$_2$O (median 149·6) Although each of these groups differs significantly ($P<0{\cdot}02$) there is considerable overlap. The anus was gaping in 17 subjects and closed in 34 (in two patients this was not recorded). The pressure profiles were 6·8–156 cmH$_2$O (median 31) and 13·6–177 cmH$_2$O (median 88·4) respectively Again the difference is significant ($P<0{\cdot}02$) but the overlap considerable.

Physical examination whether by finger or appearance was therefore shown to give a very poor assessment of anal pressure.

Defunctioned proctitis: a diagnostic dilemma

M.C. Winslet and M.R.B. Keighley, *The General Hospital, Birmingham, UK*

Proctitis in the defunctioned rectum may represent a normal physiological response or the onset of inflammatory bowel disease It is a common indication for not restoring intestinal continuity The aim of this study was to investigate the cause, diagnostic criteria and effect of restoring intestinal continuity in this condition.

Eighteen patients underwent diversion and 10 had intestinal continuity restored for a non-inflammatory condition. Macroscopic inflammation occurred in 10 patients (56 per cent) within 3 months of diversion, with histological confirmation in five. Five patients showed macroscopic and histological improvement on restoring continuity There was no significant difference in mucosal indices between the proctitis (P) and non-proctitis (NP) group. (Crypt-cell production rate: P=2·5±0·7, NP=2·9±0·9 cells crypt^{-1} h^{-1}. Glucosamine synthetase. P=14·3±3·3, NP=14·7±2·6 mmol g^{-1} h^{-1}. Mucosal lymphocytes. P=1·1 × 10^{7}, NP=1·9 × 10^{7} cells g^{-1}) The flora of the excluded colon (aerobic and anaerobic species carriage rate· organisms (P=6·8^{7}, NP=3·0^{7}) and species count (P=4, NP=4)) was not significantly different in the two groups. Colonic permeability was similar (P=8·5 per cent, NP=6·1 per cent).

Defunctioned proctitis is a common complication after faecal diversion of unknown aetiology Its only diagnostic feature, to date, is resolution after restoration of continuity. Its presence is not a contraindication to stoma closure.

Function after stapled ileal pouch–anal anastomosis for ulcerative colitis

D. Marzouk, N.S. Williams and R.I Hallan, *Surgical Unit, The London Hospital, London, UK*

Mucosal proctectomy and endoanal ileal pouch–anal anastomosis leads frequently to minor leakage which has been attributed to internal sphincter damage, presumably from prolonged anal retraction A stapled pouch–anal anastomosis does not stretch the sphincter and should lead to better function

Eleven patients with ulcerative colitis (six men and five women) with a median age of 31 years (range 17–53 years) underwent ileal pouch formation and construction of a stapled anastomosis by a modified technique, which eliminated the use of purse-string sutures. Manometry and clinical evaluation were performed before and 3 months and 9 months after operation, respectively. Function was compared with our previous results achieved with mucosal proctectomy and endoanal anastomosis. Stapled pouch anastomosis was quicker to perform (3 h *versus* 5 h), but bowel frequency (6/24 h), and requirement for medication (nine patients, 90 per cent) were similar to those achieved after proctectomy and endoanal anastomosis. Continence was only marginally superior, with seven patients entirely continent, two with occasional nocturnal leakage and two with moderate leakage. The resting anal pressure and maximum squeeze pressures were 75 (52–110) and 140 (26–350) cmH$_2$O, respectively, before operation, and 34 (20–60) cmH$_2$O ($P<0{\cdot}01$, Mann–Whitney U test) and 93 (14–190) cmH$_2$O after operation, the latter figure being not significantly different

Thus, although a stapled anastomosis is quicker to perform than the conventional technique, and may lead to improved continence, it causes damage to the internal anal sphincter This must be due to a mechanism other than anal retraction. Further functional improvement is only likely if this damage can be identified and avoided.

Faecal challenge as a predictor of the effect of restoring intestinal continuity in defunctioned Crohn's colitis

M.C. Winslet and M.R.B. Keighley, *The General Hospital, Birmingham, UK*

The effect of restoring intestinal continuity in patients with defunctioned Crohn's colitis is unpredictable. The aim of this study was to assess whether preoperative faecal challenge of the defunctioned colon with ileostomy effluent can predict those patients likely to suffer an early relapse.

Nine patients (four men and five women, mean age 39 years) with Crohn's colitis, admitted for restoration of intestinal continuity, had a mean volume of 120 ml (range 60–280) ileostomy effluent inserted into the efferent limb of their loop ileostomy daily for 7 days. The time to defaecation was 1(1–2) day. Four patients developed diarrhoea (5–10 times a day) with systemic symptoms and were considered unsuitable for stoma closure. Two patients developed mild diarrhoea whilst three were asymptomatic. Five patients had intestinal continuity restored and all remain in clinical remission at 6 months.Changes in serum and mucosal indices of disease activity after faecal challenge and restoration of continuity was similar. Faecal challenge produces results similar to restoration of intestinal continuity. It is a useful method of predicting patients likely to suffer an early relapse in whom intestinal continuity should be avoided.

	Defunctioned	Faecal challenge	Intestinal continuity
Modified activity index	99±7	118±8*	115±6*
Albumin (g/l))	40·7±1·2	39·5±1·3	398·8±1·0
α_1-Antichymotrypsin (g/l)	0·65±0·1	0·77±0·1	0·8±0·1****
α_1-Acid glycoprotein (g/l)	1·07±0·2	1·31±0·2*	1·46±0·2****
Glucosamine synthetase (mmol/g wet weight per day)	16·5±2·7	28·1±4·9***	28·5±4·6**

* $P<0.05$; ** $P<0.02$, *** $P<0.01$; **** $P<0.001$

A clinical index to assess treatment of perianal Crohn's disease

A. Allan, L. Linares and J. Alexander-Williams, *Department of Surgery, The General Hospital, Birmingham, UK*

The treatment of the perianal complications of Crohn's disease is empirical and the results are assessed subjectively. A simple clinical index of perianal Crohn's disease (PACD) would allow quantification of the efficacy of surgery or medical treatments.

Forty patients with PACD and 14 patients with other anal pathology were studied. A linear analogue score (LAS) was used to record seven clinical parameters before and after surgical treatment. These included perianal pain, pruritus ani, inhibition of locomotion, social and sexual activity, pain on defaecation and anal leakage. The Mann–Whitney *U* test was used to determine differences in LAS before and after treatment.

Therapy	Number of patients	LAS before treatment	LAS after treatment
Patients with PACD			
Drain perianal abscess	25	3·9 (1·9–6·4)	0·6 (0–5·7)‡
Other minor anal surgery	7	3·3 (2·3–5·3)	1·6 (0–2·0)‡
Loop ileostomy or proctectomy	5	2·4 (1·6–6)	0 (0·04)†
Continual drug therapy	3	2·3 (2·3–2·5)	0·4 (0·3–1·4)§
Patients with other anal pathology			
Haemorrhoidectomy	10	2·8 (1–4·8)	0·2 (0–0·8)†
Drainage of perianal abscess	4	4·6 (1·2–7·2)	0·2 (0–1·2)*

Results are shown as median (ranges)
* $P<0.05$, † $P<0.01$, ‡ $P<0.001$, § not significant

This simple clinical index of PACD is sensitive to changes in disease state brought about by surgical or medical therapy. It has potential for prospective comparison of rival treatments of PACD.

The role of the faecal stream in maintaining the inflammatory process in Crohn's colitis

M.C. Winslet, A. Allan and M.R.B. Keighley, *The General Hospital, Birmingham, UK*

The remission rate in Crohn's colitis treated by ileostomy alone (82 per cent, $n=44$) implicates a faecal constituent in disease pathogenesis. Faecal diversion provides an alternative to resection and also a model to investigate the role of the faecal stream. The effect of diversion and restoration of continuity on clinical (MDAI), blood (haematological/acute phase proteins) and mucosal (histological/cell birth rate/mucous-Ig production glucosamine synthetase activity) indices of disease activity was assessed in patients with Crohn's colitis (diversion 22, continuity 10) and in controls with a non-inflammatory condition (diversion 13, continuity 8) with reference to changes in colonic microflora and permeability.

In Crohn's colitis, after faecal diversion there was a fall in MDAI from 176±9 to 114±9 ($P<0.01$); in acute phase proteins from 1·9±0·2 to 1·1±0·1 g litre^{-1} ($P<0.01$), and in glucosamine synthetase activity from 31·9±3·4 to 24·8±3·6 mmol g^{-1} h^{-1} ($P<0.01$). Restoration of continuity produced an increase in acute phase proteins from 1·1±0·1 to 1·5±0·2 ($P<0.05$) and in glucosamine synthetase activity from 14·7±2·6 to 27·3±3·7 ($P<0.01$). There was no difference in the mucosal/luminal qualitative or quantitative aerobic/anaerobic flora after faecal diversion. Colonic permeability (^{51}Cr-EDTA) increased from 6·2±2·7 to 27·8±4·2 per cent ($P<0.05$) after faecal diversion.

This study implicates the faecal stream in the inflammatory mechanism of Crohn's colitis. It suggests that post-diversion remission is mediated by exclusion of a non-bacterial component. Faecal challenge of the defunctioned colon may determine the role of individual constituents.

Percutaneous angioscopic assessment of the immediate effects of laser and dynamic angioplasty in total peripheral arterial occlusions

S. Ashley, A.A. Gehani, G.A. Davies, R.C. Kester and M.R. Rees, *Cardiac Research Unit, Killingbeck Hospital, Leeds, UK*

High-resolution, ultrathin, flexible fibreoptic angioscopes (Olympus PF 1·4 mm and 1·8 mm outer diameter), have been used via a No. 8 Fr percutaneous angiographic guiding sheath, to assess the immediate effects of angioplasty in 10 patients with 12 total peripheral arterial occlusions. This group included three patients with reocclusions following previous angioplasty procedures. There were 10 femoral and two iliac lesions, ranging from 1 to 15 cm in length. Angioplasty was performed with either a No. 8 Fr fast-rotating tip atherectomy catheter (Kensey) ($n=6$), continuous wave Nd-YAG laser (Surgical Laser Technologies CL 60) delivered by fibres with 2·2 mm hemispherical sapphire distal tips ($n=3$), or balloon angioplasty alone ($n=3$). A clear view was successfully obtained in 10 out of 12 vessels by displacing flowing blood with a pressurized heparin/saline flush. The total volume of fluid administered intra-arterially ranged from 300 to 1000 ml. A video recording of each procedure was made via a micro-chip camera (Olympus OTVF).

Angioscopy was performed to identify intimal flaps after all angioplasty procedures. After mechanical angioplasty in two patients, the detection of large obstructive flaps led to additional laser therapy to improve blood flow. Angioscopy has demonstrated effective percutaneous laser ablation of thrombus and atheromatous plaque. Small areas of intimal charring were seen after laser delivery, but there were no vessel-wall perforations. Angiography was undertaken in all patients and compared with angioscopy. The above features were either not demonstrated or poorly demonstrated by angiography. There were no embolic complications or problems related to fluid overload.

Thermographic and electron microscopic analysis of integral optical fibre tips for pulsed laser angioplasty

A. Murray and R.F.M. Wood, *Surgical Unit, St Bartholomew's Hospital, London, UK*

Studies of laser angioplasty with the metal-capped ('hot-tip') probe have shown that the tip temperature of 400°C produces widespread thermal damage. To overcome this we have developed an integral spherical tip to be used with pulsed lasers. This study defines their thermal characteristics.

An Agema Thermovision-870 infrared camera imaged a series of six fibreoptic probes in air and during laser ablation of arterial wall *in vitro*. Each probe comprised a 2 m length of 0·6 mm diameter quartz expanded into a 2·5 mm sphere, three were precision ground to produce a 2 mm diameter flat face. Laser energy was produced by a Pulsed Dye laser (wavelength 480 nm, 1 μs pulses). The peak temperature reached only 48°C in air and that of the ground tip was significantly less than that of the spherical ($P<0.01$), though the reverse was found when ablating arterial wall ($P<0.01$). This difference was lost when the laser tip was in direct tissue contact. The highest temperatures were attained with atheroma (130°C). After prolonged use of the laser with the tip in contact, tips attained higher temperatures in air than when new. Scanning electron microscopy revealed surface pitting and fissuring in these cases Initial temperature characteristics were regained after regrinding The surface damage of the tip is likely to be due to plasma production associated with pulsed ablation, leading to light scatter and higher tip temperatures

We conclude that use of the pulsed laser with integral fibre tips does not attain the excessive temperatures reported with metal-capped probes and will therefore minimize vessel wall damage and lessen the risk of perforation.

A vein collar/patch optimizes patency rates in PTFE grafts

M.R. Tyrrell, J.F. Chester*, R.S Taylor* and J.H.N. Wolfe, *St. Mary's Hospital and Irvine Cardiovascular Laboratory, London and *Epsom District Hospital, Surrey, UK*

The results of polytetrafluoroethylene (PTFE) grafts to crural vessels have been sufficiently poor for some surgeons to consider primary amputation for critical ischaemia in the absence of suitable autologous vein. However, the results of two anastomotic techniques using a short segment of interposed vein[1,2] are encouraging

We have attained 1-year actuarial patency rates of 47 per cent ($n=27$) using PTFE with Miller collar anastomoses to distal crural vessels, and 84 per cent ($n=45$) using the Taylor patch technique[3]

To investigate the haemodynamic benefit of these techniques, we have tested them (using a pulsatile flow model[4] incorporating standard pressure, viscosity, graft and vessel length, and anastomotic angle) against a standard end-to-side PTFE anastomosis to cadaveric internal mammary artery There was no significant difference in flow between the anastomotic methods. Downstream resistance was dictated by the diameter of the vessel, provided a vein interposition technique was used ($r>0·70$), but this relationship was lost if a direct PTFE/arterial anastomosis was performed ($r=0·04$), suggesting additional anastomotic resistance in the latter.

In conclusion, this constitutes experimental evidence to support the hypothesis that these vein-interposition techniques confer haemodynamic benefit in the use of PTFE.

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The effects of cigarette smoking, carbon monoxide and nicotine on the uptake of ^{125}I-labelled fibrinogen by the canine arterial wall

D.R. Allen, N.L. Browse and D.L. Rutt, *St Thomas' Hospital, London, UK*

Permeability of the arterial wall of anaesthetized dogs has been shown to be increased by inhaling cigarette smoke or carbon monoxide (CO) but not by intravenous nicotine. These experiments describe the effect of cigarette smoke, CO and nicotine on the amount of ^{125}I-labelled fibrinogen retained within the arterial wall.

Four groups were studied: a control group (6 arteries); a smoking group (6 arteries) who inhaled 20 cigarettes over 5 h; a carbon monoxide group (8 arteries) who inhaled 400 p.p.m CO over 5 h, and a nicotine group (8 arteries) who received intravenous nicotine 2·5 μg kg^{-1} min^{-1} for 5 h. Carboxyhaemoglobin, plasma nicotine and arterial pressure were monitored in all groups Two hours after commencing the experiment, ^{125}I-labelled fibrinogen was injected intravenously Plasma radioactivity was recorded every 30 min for 3 h to calculate plasma decay. A 3 cm length from each carotid artery was then excised, the adventitia removed and, after homogenization, the artery wall was resuspended in 2 ml saline and radioactivity counted in a well-counter. Wall uptake was calculated by dividing the wall count by the plasma count.

	Control	Smoking	CO	Nicotine
Wall uptake units × 10^{-4} ± s.e.m.	4·5 ± 1·4	5·5 ± 2·8	6·1 ± 2·7	9·1 ± 2·1

$P<0·001$ (unpaired t test)

The results showed that whereas intravenous nicotine did not increase the permeability of the arterial wall to fibrinogen, it did increase the amount of fibrinogen retained within the arterial wall

Is thrombocytopenia after aortic surgery related to salvage autotransfusion?

J.F. Thompson, the late P.C. Clifford, J.H.H. Webster and A.D B. Chant, *Vascular Unit, Royal South Hants Hospital, Southampton, UK*

Haemostasis is dependent on adequate numbers of functional platelets A transient fall in platelet numbers has been described following salvage autotransfusion (ATS)[1] and platelet activation occurs during cardiopulmonary bypass[2] ATS involves extracorporeal circulation and these factors may be implicated in postoperative bleeding

To investigate these effects 50 consecutive patients (mean age 69 years) undergoing elective aortic reconstruction have been studied. Twenty received bank blood (controls), 20 ATS (non-washed) and ten ATS (cell-saver).

Blood samples were taken preoperatively and at 0 h, 4 h, 24 h and 1 week postoperatively Platelet counts were performed using a laser particle counter. To measure the overall integrity of the haemostatic mechanism, template bleeding times (Simplate-II, single observer, with venous occlusion) were performed preoperatively and at 4 h. This avoided the contribution of residual heparin and anaesthetic agents

There was no morbidity related to postoperative bleeding.

Table 1 *Platelet count*

	Platelets × 10^9 litres (mean and s.e.m.)		
	Controls	Non-washed	Cell-saver
Preoperative	244 (16·4)	250 (11·0)	216 (12·4)
0 h	175 (10·4)	172 (13·0)	158 (17·0)
4 h	149 (10·2)	165 (13·0)	169 (25·0)
24 h	131 (9·6)	145 (9·8)	135 (11·8)
1 week	221 (18·0)	280 (18·0)	228 (10·0)

All differences non-significant by Wilcoxon test

Table 2 *Bleeding times*

	Controls (s)	Non-washed (s)	Cell-saver (s)
Preoperative	207 (15·9)	226 (24·0)	195 (16·0)
Postoperative	301 (18·3)	314 (24·2)	270 (27·7)

Salvage ATS does not appear to contribute appreciably to the fall in platelet count seen after aortic surgery In this series, ATS by either technique did not give rise to a significant bleeding diathesis.

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Prazosin reduces the development of atherosclerosis in rabbit aorta

M.K. O'Malley, D. Hehir, J. O'Byrne, D. Mehigan and N.J. O'Higgins, *Department of Surgery, University College, Dublin, Ireland*

Earlier studies have demonstrated that prazosin, a selective α_1-adrenergic antagonist, reduces the development of intimal hyperplasia in rabbit aorta[1]. Intimal hyperplasia is thought to be a precursor for atherosclerosis and so we have examined the effect of prazosin on atherogenesis Atherosclerosis was induced in 32 New Zealand white rabbits with a 1 per cent cholesterol diet either alone or in combination with endothelial denudation of the aorta using a Fogarty balloon catheter. Test rabbits were given 4 mg prazosin orally commencing on the morning of surgery and continuing until they were killed 8 weeks later The aortas were then harvested, opened longitudinally and stained with Sudan IV to demonstrate atherosclerotic plaques. Photographs of the intimal surface were enlarged and an x–y digitizer was used to measure the percentage of aortic intima affected by atherosclerosis.

	Diet alone ($n=8$)	Diet + prazosin ($n=8$)	Diet + denudation ($n=8$)	Diet + denudation + prazosin ($n=8$)
Percentage aortic atherosclerosis (mean ± s.e.m.)	38·8 ± 6·2	28·1 ± 3·1	60·5 ± 2·3	49·3 ± 4·3
	P = n.s.		$P<0·05$	

The results show that prazosin significantly reduces the development of atherosclerosis in denuded rabbit aorta and may also reduce atherogenesis in normal rabbit aorta. These results further support the use of prazosin in reducing the complications of endothelial denudation[1,2].

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Non-invasive determination of concomitant coronary artery disease in patients with intermittent claudication

A-M. Salmasi and A.N. Nicolaides, *Irvine Laboratory for Cardiovascular Investigation and Research, Academic Surgical Unit and Vascular Unit, St. Mary's Hospital Medical School, London, UK*

The association between intermittent claudication and concomitant coronary artery disease (CAD) is well recognized. The ECG chest wall mapping stress test (CWM), which can detect the presence of coronary artery disease in individual coronary artery territories[1], has been used in 100 consecutive patients with intermittent claudication. ECG recordings from all the leads were carried out at rest, each minute during exercise, at peak exercise and each minute after terminating the exercise until the heart rate and blood pressure returned to pre-exercise values. Areas of significant ST segment changes (elevation or depression), inverted U-waves and resting Q-waves were determined and assigned to individual coronary artery territories.

The exercise testing was positive in 47 patients. It suggested significant single coronary artery disease in six, double in 16 and triple in 25 patients. Coronary arteriography was carried out in 34 of 47 patients with a positive stress test. Significant CAD (>50 per cent stenosis in at least one coronary artery) was present in all the 34 patients. The predictive accuracy of CWM to detect the number of coronary arteries with significant stenosis was 84 per cent while the predictive accuracy in diagnosing a significant lesion in an individual coronary artery territory was 92 per cent. On clinical grounds the presence of CAD was suspected in 21 of the 47 patients with a positive stress test. Thus, occult CAD was present in 26 patients, which was confirmed later by coronary arteriography; 12 of these had significant disease in three coronary artery territories. The results confirm the high incidence of severe coronary artery disease in claudicants and indicate the values of this non-invasive screening test in patients with intermittent claudication.

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Erythrocyte fatty acid changes in the diagnosis and postoperative follow-up of patients with colorectal carcinoma

S.B. Kelly, N.A. Habib, M. Lucarotti, J. Beynon, C.B. Wood* and R.C.N. Williamson*, *Departments of Surgery, Bristol Royal Infirmary* and **Royal Postgraduate Medical School, London, UK*

The stearic to oleic acid ratio (saturation index) of erythrocytes has been found to be significantly lower in patients with malignant disease compared with patients with benign diseases and normal healthy subjects. Similar changes have also been observed in solid tumour tissue and leukaemic cells. The aim of this study was to investigate whether the erythrocyte saturation index could be useful as a marker for patients with colorectal carcinoma. Blood samples were obtained from normal healthy subjects and patients with colorectal carcinoma, recurrent colorectal carcinoma, inflammatory bowel disease, and benign colonic polyps. Total lipids were extracted from the erythrocytes and the fatty acids were analysed by gas–liquid chromatography. The ratio of stearic to oleic acid was taken as the saturation index (SI).

Group	Number	SI mean ± s.e.m.
Normal subjects	107	1·18 ± 0·02
Inflammatory bowel disease	18	1·25 ± 0·06
Benign colonic polyps	18	1·20 ± 0·06
Colorectal carcinoma	97	0·97 ± 0·02
Recurrent colorectal carcinoma	21	1·01 ± 0·05

This study confirms that the erythrocyte saturation index is lower in patients with colorectal carcinoma ($P<0·001$) and recurrent colorectal carcinoma ($P=0·003$–$0·01$) than in normal healthy subjects or patients with various benign diseases. In addition, the index returns to normal (mean 1·14 ± 0·03, $n=33$) at 3 months postoperatively in patients who remain disease-free following curative resection ($P<0·001$). Thus, the erythrocyte saturation index may be useful in the diagnosis and postoperative monitoring of patients with colorectal carcinoma.

Tumour cell-mediated suppression of lymphokine-activated killer cell generation is associated with the release of soluble suppressor factors from tumour cells

S.S. Somers, C.W. Ramsden, P.C. Sedman and P.J. Guillou, *University Department of Surgery, St James's University Hospital, Leeds, UK*

Adoptive immunotherapy of patients with metastatic tumour using autologous lymphokine-activated killer (LAK) cells and interleukin 2 (IL-2), is successful in only 40 per cent of patients. The impaired LAK generation in patients with advanced disease may be due to direct interference with LAK stimulation by tumour cells, as therapy with IL-2 alone is ineffective.

The possible immunosuppressive effects of tumour-cell products were investigated using serum-free supernatants from the following cell lines: G361 (melanoma), COLO 205, COLO 320, HT-29 (colorectal cancers), MiPaCa (pancreatic cancer), SKBr3 (breast cancer), WISH (human amnion) and normal endothelium. Normal human peripheral blood mononuclear cells were incubated for 4 days with 1000 units/ml IL-2 in the presence of 20 per cent supernatant from an individual cell line. LAK cytotoxicity (lytic units) was measured on the fourth day of culture. The results are shown in the *Table*.

Source of supernatant	Target cell	Inhibition of lytic units (%)
G361	G361	99·9
COLO 320	COLO 320	62·1
COLO 205	COLO 205	99·9
HT-29	G361	99·9
MiPaCa	G361	92·1
SKBr3	SKBr3	−3·0
WISH	SKBr3	−40·0
Normal endothelium	SKBr3	−5·0

This suppression of LAK generation was time-related and dose-related. Generation of LAK cytotoxicity was inhibited by supernatant concentrations as low as 5 per cent but inhibition of proliferation was only seen with higher concentrations. The inhibitory component is stable on heating to 56°C but not to 70°C, is acid-labile and has a molecular weight greater than 25 000. The metabolic inhibitors mitomycin C, Adriamycin® (Farmitalia Carlo Erba, UK) and cycloheximide, diminish the production of the suppressive component by cell lines. Tumour cell-mediated inhibition of LAK cell function may, in part, explain the therapeutic failure of adoptively transferred LAK cells and IL-2 in humans.

Microendoscopy in the diagnosis of anal dysplasia

J.H. Scholefield, C. Sonnex, C. Whatrup and J.M.A. Northover, *ICRF Unit, St. Mark's Hospital and The Middlesex Hospital, London, UK*

Evidence that sexually transmissible types of human papillomavirus (HPV) are important in the aetiology of cervical neoplasia is increasingly convincing[1]. We have demonstrated an association between the same HPV types (16 and 18) in anal squamous cell carcinoma in a series of cases.

In a preliminary series we have examined 50 patients, 20 normals and 30 with perianal warts. We have used a colposcope to look for subclinical dysplastic anal canal lesions equivalent to those described in the cervix. A 5 per cent acetic acid solution has been used to highlight these lesions. We have identified areas of anal intraepithelial neoplasia (AIN) in anoscopic biopsies from eight patients. DNA hybridization has detected HPV type 16 DNA in 2/8 of the AIN lesions. Subclinical anal wart virus infection was seen in addition to macroscopic warts in 24/30 wart patients.

These findings suggest that anal microendoscopy is a useful tool in the diagnosis of the subclinical anal manifestations of wart virus infection and we are continuing to assess its use in the diagnosis of dysplasia.

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Biodegradable emboli increase the delivery of cytotoxic drug to hepatic tumours

D. Chang, S.A. Jenkins, D M. Nott, S. Grime and T. Cooke, *University Department of Surgery, Royal Liverpool Hospital, Liverpool, UK*

Degradable starch microspheres (DSM) combined with regional chemotherapy are being evaluated in patients. We have investigated whether DSM enhance delivery to tumour of both Adriamycin® (Farmitalia Carlo Erba, UK), which is actively taken up by hepatocytes, or a low molecular weight marker which is not.

In a rat model of hepatic metastases the optimum dose of DSM to minimize the passage of the relatively non-diffusable ^{99m}Tc-methylene diphosphonate (MDP) was established. ^{14}C-labelled Adriamycin alone and with DSM (half-life 20 min) was injected via the hepatic artery and its distribution determined after 90 min. In further studies MDP was injected with and without DSM and animals were killed immediately or after 90 min.

Adriamycin is preferentially retained in liver with a tumour to normal tissue ratio of 1 88±0·65 ng/mg 6 60±0 38 ng/mg ($P<0·001$ Mann–Whitney *U*) Concomitant injection with DSM increased tumour retention threefold to 7·87±0·7 ng/mg without affecting normal liver uptake (8 32±0 08 ng/mg) The tumour to liver ratio for MDP alone was 0 61±0 04.0·79±0·07 and DSM gave an immediate significant increase in this ratio to 26 03±2·81:8·67±0 81 ($P<0 001$) which was maintained at 90 min after complete degradation of DSM with a 14-fold retention in tumour (11 11±1 08:0 69±0 08, $P<0 001$)

DSM enhance hepatic tumour uptake of both a non-diffusable marker of similar molecular weight to common cytotoxic drugs, and a drug actively metabolized by hepatocytes, confirming its potential clinical benefit.

Changes in cell cycle kinetics during experimental colonic carcinogenesis

T. Cooke and J. Matthews, *Departments of Surgery, Royal Liverpool Hospital and Charing Cross Hospital, London, UK*

Crypt-cell production rate increases with the induction of colonic carcinogenesis[1] and we have investigated the mechanism of this.

Rats, administered the carcinogen azoxymethane or saline (as a control) subcutaneously for 12 weeks, were given vincristine 1 mg/kg intraperitoneally to arrest cells in metaphase at week 25, and were killed at 15-min intervals Metaphases were counted in the descending colon in 100 crypts per animal, expressed as a percentage of total crypt counts and plotted against time Entry into mitosis was calculated from the slope of the resulting regression line and cell cycle time derived as its reciprocal

There was a significant hyperplastic response in the carcinogenic rats compared with controls, increasing from 36·69±2 71 to 48 84±4·64 cells/crypt ($P<0·001$). The proliferation zone increased from 23 to 29 cells although the proportion of dividing cells (growth fraction) did not alter between controls (0·62) and carcinogenic groups (0 59) In the latter the rates of entry into mitosis decreased significantly from control values of 6·48 to 3·84 per cent of cells h^{-1} ($P<0 01$). Overall cell cycle time (T_c) increased from 30·86 h to 59·09 h; the T_c in stem cells was significantly reduced from control values of 112·0 h to 47·3 h ($P<0 01$) whereas, in contrast, the T_c in the proliferative compartment rose from 30·86 h to 66 4 h ($P<0 01$).

Absolute increases in the numbers of proliferating crypt cells, despite a slowing down of cell division, explains the previously observed elevation in crypt-cell production rate[1], advancing our understanding of the mechanism of colonic carcinoma development and may explain, in part, the failure of cytostatic therapy.

1 Cooke T, Kirkham N, Stainthorpe DH *et al.* Detection of early neoplastic changes in experimentally induced colorectal cancer using scanning electron microscopy and cell kinetic studies *Gut* 1984, **25**· 748–55

Host anti-tumour defences are not directly inhibited by lymphocyte circulation through the primary tumour

J.R T. Monson, W. Maxwell, P.W.N. Keeling, R.B. Stephens, F.B.V. Keane and W. A. Tanner, *Department of Surgery, Trinity College, Dublin, Ireland*

Some patients with gastrointestinal cancer have impaired cellular immune responses Colonic tumours produce excessive amounts of the immunosuppressive prostaglandin PGE$_2$. This study addresses the possible connection between these two findings by measuring lymphocyte function before and after *in vivo* circulation through colonic tumours

Blood was taken from both the arterial and venous systems of colonic tumours at the time of operation ($n=14$). Samples were assayed for lymphocyte transformation (using concanavalin A), T-cell subsets, interleukin 2 production, natural killer (NK) activity and lymphokine-activated killer (LAK) cell generation

	Lymphocyte transformation	IL-2 production	NK activity	LAK activity
Arterial	22441±3192	3 1±1 2	86 1±21 2	68 6±14 6
Venous	23022±3603	3·9±0·9	56 0±17·8	61 0±16·4

Lymphocyte transformation is measured in counts per minute; interleukin 2 production in units per millilitre; natural killer and lymphokine-activated killer activities in lytic units.

The results (mean±s e m.) revealed no difference between levels of lymphocyte function before and after the cells passed through the primary tumour. In addition there was no difference in the percentages of T-cell subsets between venous and arterial blood The results were unaffected by the Dukes' stage of the primary cancer

These data indicate that the immunosuppression exhibited by patients with gastrointestinal cancer may not be due to a locally exerted effect of the primary tumour and do not support regional perfusion of tumours with interleukin 2 However, further studies are now required in control subjects and those with benign colonic disease

Inhibition of colonic carcinogenesis by stearic acid in rats

S.B. Kelly, N.A. Habib, C B. Wood* and R C.N Williamson*, *Departments of Surgery, Bristol Royal Infirmary and *Royal Postgraduate Medical School, London, UK*

Malignant transformation of the cell reduces the stearic to oleic acid ratio in its cell membrane, thus decreasing membrane rigidity and increasing cell metabolism and proliferative activity Stearic acid has been shown to inhibit mammary carcinogenesis in rats Potential inhibition of colorectal carcinogenesis by stearic and oleic acid was tested in 72 male F344 rats which were allocated to one of four groups. (1) azoxymethane (AOM) alone, (2) AOM plus liquid paraffin, (3) AOM plus stearic acid and, (4) AOM plus oleic acid in liquid paraffin. AOM was administered by six weekly subcutaneous injections (15 mg kg^{-1} $week^{-1}$). Starting 1 week after the last AOM injection, the fatty acids were injected subcutaneously twice weekly at a dose of 25 mg in 0 5 ml liquid paraffin.

Group		Survival (weeks)	Small bowel tumours	Large bowel tumours
Control	($n=18$)	37 9±1·4*	1·1±0 2	1 5±0·2
Liquid paraffin	($n=18$)	36·3±1·2*	1 3±0·3	1·6±0 4
Oleic acid	($n=18$)	35·2±2·0	0 7±0·2	1 4±0 4
Stearic acid	($n=18$)	>45·3±1 2	0 3±0 3	1 5±0·7

All figures are means±s.e m.
Significance versus stearic acid *$P<0 001$

By week 44, all rats in the control and oleic acid groups were dead with tumour. By contrast, 11 of 18 rats in the stearic acid group are still alive and apparently tumour-free at 48 weeks There was no significant difference in survival between the control and the oleic acid groups In addition, the number of tumours in the small bowel and large bowel did not differ significantly between the groups. These results indicate that stearic acid prolongs survival in rats undergoing colonic carcinogenesis with azoxymethane.

Natural killer (NK) cell function: is the colon an immunosuppressive organ?

G. Jacob, L. Rawlinson, R C. Rees* and K. Rogers, *University Departments of Surgery and *Virology, Sheffield, UK*

The origin of reduced NK cell function in malignant disease is obscure. We have studied the effect of colonic vascular transit on NK cell cytotoxicity and the immunosuppressive activity of colonic venous plasma in patients with benign or malignant intra-abdominal disease

Heparinized blood (20 ml) was obtained from a peripheral vein, the aorta and colonic mesenteric veins in patients undergoing elective surgery for colonic carcinoma ($n=29$) or non-malignant disease ($n=13$) NK cells were harvested by a standard technique[1] and cytotoxicity assessed by a 4 h chromium-51 release assay using the K562 leukaemic cell line as the target With the same target the kinetics of NK cytotoxicity were studied by a single cell assay using plasma from the same patients[2] and lymphocytes from healthy donors.

Overall, colonic transit had no significant effect on NK cell cytotoxicity but in some patients enhancement ($n=6$) or suppression ($n=7$) was noted. However, colonic venous plasma proved suppressive to NK-mediated cytolysis, both from patients with benign and malignant disease

Table 1 *Host NK cell cytotoxicity (%) to K562 leukaemic cell line*

	Arterial	Tumour venous	Colon venous	Peripheral venous
Carcinoma ($n=29$)	28±15	26±14	25±15	23±12
Benign ($n=13$)	26±17	—	29±19	26±20

Table 2 *Immunosuppression by host plasma of donor NK cell cytotoxicity (%) to K562 leukaemic cell line*

	Autologous	Arterial	Tumour venous	Colon venous	Peripheral venous
Carcinoma ($n=29$)	36±13	29±11	21±11*	21±11*	30±09
Benign ($n=13$)	34±06	27±10	—	20±08*	27±10

All values as mean±1 s d *$P>0\cdot001$ t-test

In conclusion colonic vascular transit has no consistent effect on NK function but colonic venous plasma contains an unidentified, soluble immunosuppressant This factor acts at a post-recognition phase of the cytotoxic process and further studies are required for its characterization.

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Endotoxaemia in experimental obstructive jaundice and following its relief by internal and external biliary drainage

T Diamond, R.L E. Thompson, E McGlone and B J. Rowlands, *Department of Surgery, The Queen's University of Belfast, UK*

Endotoxaemia has been demonstrated in experimental models and patients with obstructive jaundice and is associated with postoperative renal failure, sepsis and haemorrhagic gastritis. It is postulated that absence of intraluminal bile salts predisposes to portal absorption of gut endotoxin and that endotoxaemia is reversed by oral bile salt therapy, or internal biliary drainage and return of bile salts to the gut, but not by external biliary drainage We believe that relief of biliary obstruction and restoration of normal hepatocyte and Kupffer cell function is a more important contributing factor to the reversal of endotoxaemia than restoration of gastrointestinal (GI) bile flow. The aim of this study was to determine the relative roles of biliary obstruction and GI bile flow in the development and reversal of endotoxaemia.

Portal and systemic endotoxin concentrations were measured using a quantitative Limulus assay in control rats, 2 weeks after bile duct ligation (BDL) and 2 weeks later after relief of biliary obstruction by internal drainage (ID. choledochoduodenostomy) or sterile external drainage (ED choledochovesical fistula[1])

	Portal endotoxin mean±s e m. (pg/ml)	Systemic endotoxin mean±s e m (pg/ml)
Controls ($n=10$)	224±85	240±77
BDL 2 wks ($n=15$)	1304±129*	918±110*
BDL 2 wks+ID 2 wks ($n=8$)	442±87	328±67
BDL 2 wks+ED 2 wks ($n=8$)	383±165	376±94

Significance *versus* controls· * $P<0\cdot005$, bilirubin was elevated in BDL (201±12 μmol/litre) compared with controls, ID and ED (Mann–Whitney U test)

It was concluded that significant portal and systemic endotoxaemia occurred in BDL compared with controls Relief of biliary obstruction by both internal and external drainage reversed portal and systemic endotoxaemia This confirmed that relief of biliary obstruction is a more important factor than restoration of intraluminal GI bile flow in the reversal of endoxaemia

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Enhancement of mucosal cell migration in experimental gastric stress ulceration.

R. Stuart, T.F. Gorey, R. Flynn, S. McBennett, E. Kay, P. Byrne and T P.J Hennessy, *Trinity College Dublin Department of Surgery, St. James's Hospital, Dublin, Ireland*

Mucosal ulceration is the result of an imbalance between ulcerogenic and protective elements, one of which is the ability of mucosal cells to replicate and restore surface continuity To study this restitution process nuclear DNA was radiolabelled with tritiated thymidine, and after autoradiography a labelling index was calculated from the ratio of labelled to total cells, and their migration position was measured along the length of the gastric gland. Two groups each of 24 Wistar rats (mean weight 85·2±4·3 g) were studied immediately and 48 h after cold restraint stress which caused histologically proved mucosal ulcers Thymidine uptake and cell position, indicating mitotic and migration rates, were assessed in 20 glands per animal for a representative 100 labelled cells in each of four groups controls ($n=9$), stress, untreated ($n=5$); stress, with cimetidine prophylaxis ($n=5$), and stress, with allopurinol prophylaxis ($n=5$) The table shows total labelling and cell position indices immediately and (in parentheses) 48 h after stress

Cell position	Normals	Untreated stress	Cimetidine	Allopurinol
Surface	6·13 (24·69)	6·33 (10·3)	9·29 (25·41)*	14·00* (12·42)
Proliferative zone	16·81 (16·35)	12·58† (9·89)	16·19 (12·88)	15·43 (10·73)
Percentage of total labelled	8·43 (13·09)	5·31 (7·17)	7·03* (10·44)	7·84* (6·40)

* $P<0\cdot001$ *versus* untreated stress; † $P<0\cdot001$ *versus* normals, unpaired Student's t test

Immediately after stress, total labelling indices show a depression of cell division while cell position index shows enhanced surface migration, allopurinol was most effective in promoting early proliferation and migration After 48 h, migration is greatest with cimetidine while lower indices in the allopurinol group may represent intraluminal shedding of already migrated cells.

Endothelial cell seeding: the influence of different luminal coatings on initial cell attachment to polytetrafluorethylene vascular grafts

J.S. Budd, R.F.L James and P.R.F. Bell, *Department of Surgery, University of Leicester, Leicester, UK*

The creation of a biocompatible, intravascular prosthesis may ultimately require a surface covered with endothelial cells that are actively antithrombogenic. In humans, however, the number of cells available for seeding is small, and in order to achieve any benefit from endothelial cell seeding the vast majority of harvested cells need to attach in a relatively short time period We have examined the role of different surface coatings in enhancing endothelial cell attachment to polytetrafluoroethylene (PTFE) vascular grafts.

Human umbilical vein endothelial cells were harvested by collagenase digestion and labelled with indium-111 oxime. The cells were then inoculated on to small segments of PTFE graft material which was either uncoated, or coated with gelatin, collagen, or fibronectin. At 30, 60 and 120 min the surfaces were washed and the radioactivity in the washings and on the graft segment was measured. Cell attachment was measured as a percentage of the initial inoculum

	Control	Gelatin	Collagen	Fibronectin
30 min	7·46±0 87	9·29±0·91*	37 00±2·57*	53·16±3 21*†
60 min	10·41±1·78	22·48±3 46*	40 76±2·38*	59 78±1 84*†
120 min	14·86±2 34	31·16±5 46*	46·22±2 97*	60 81±3 00*‡

Data are mean±s.e.m.; * $P<0\ 01$ *versus* control; † $P<0\ 01$, ‡ $P<0\ 05$ collagen *versus* fibronectin

In conclusion, pretreatment of PTFE vascular grafts with gelatin, collagen or fibronectin significantly improves the initial attachment of seeded endothelial cells Fibronectin appears to be the most effective substance in this respect

Digital or manometric assessment of anal sphincter function

R.I. Hallan and N.S. Williams, *The Surgical Unit, The London Hospital, London, UK*

Anal canal manometry is not readily available and most surgeons make management decisions based solely upon the subjective assessment of sphincter strength as felt by their right index finger. To discover whether this is an adequate measurement of sphincter function, scores (0–10) were given for the digital impression of basal and squeeze sphincter strength by one surgeon in 22 incontinent (I) and 44 continent (C) patients (22 control subjects and 22 severely constipated patients). Maximum basal (MBP) and maximum squeeze (MSP) anal canal pressures were then determined by a standard manometric station-pullthrough technique

There was a good correlation between MBP and the basal score ($r=0\ 52$, Spearman's rank correlation coefficient, $P<0{\cdot}001$) There was an even better correlation between MSP and the squeeze score ($r=0{\cdot}72$; $P<0\ 001$) MBP in incontinent patients (median 39, interquartile range 25–59 cmH_2O) was significantly lower than in the continent (72, 54–95 cmH_2O; $P<0\ 001$, Mann–Whitney U test), and this difference was detected by the basal scores (5, 3–6 I; 8, 7–9 C, $P<0{\cdot}001$). MSP in incontinent patients (43, 19–65 cmH_2O) was significantly lower than in the continent (70, 50–105 cmH_2O; $P<0\ 001$) and again this difference was detected by the squeeze score (3, 1–6 I, 8, 7–9 C; $P<0\ 001$)

It appears that assessment of anal sphincter function by the index finger of an experienced surgeon is equally as good as anal canal manometry, and is therefore adequate for most clinical purposes. Manometry nevertheless has its place in the investigation of coloproctological disorders, particularly in the setting of anorectophysiological research where objective data are required

Dietary lipids and breast carcinogenesis

G.A. Pritchard, D.L. Jones and R.E. Mansel, *Department of Surgery, University Hospital of Wales, Cardiff, UK*

Excess dietary fat is identified as a risk factor for development of breast cancer Polyunsaturated essential fatty acids (EFA) may, however, have an antitumour effect[1].

We have studied the effect of dietary fat on the growth of human breast adenocarcinoma MCF7 xenografts in athymic mice Normal chow was supplemented with corn oil or n-6 and n-3 series EFAs present in natural preparations of primrose oil and fish oil. Tumours were excised after 5 weeks and tumour mass measured.

Diet	n	Tumour mass (mg)		2P value (Mann–Whitney U)
		Median	Range	
Control	14	68	32–125	—
5% corn oil	11	68	30–152	0·84 n s
10% corn oil	14	73	28–250	0 69 n s.
20% corn oil	17	142	83–198	0 01
5% primrose oil	12	12	6–31	0 002
10% primrose oil	12	13	5–44	0 01
5% fish oil	13	45	32–78	0 31 n.s.
10% fish oil	11	15	7–34	0 004

The table shows that 5 and 10 per cent corn oil had no effect, while the high-fat diet of 20 per cent corn oil enhanced tumour growth. This is the first report of human breast tissue being responsive to fat and corroborates earlier epidemiological surveys which implied a nutritional risk factor[2] Primrose oil and fish oil supplements significantly inhibited tumour growth. Hence, nutritional intervention with EFAs may have a role as a preventive or therapeutic measure to complement existing therapies

1 Begin ME, Ells G, Das UN, Horrobin DF. Differential killing of human carcinoma cells supplemented with n-3 and n-6 polyunsaturated fatty acids *J Natl Cancer Inst* 1986, **77**: 1053–62

2. Vesset MP, Gray M, eds *Cancer Risks and Prevention* Oxford· University Press, 1985

A prospective randomized trial to compare sutures and staples in the construction of colorectal anastomoses

A.M. Akyol, J.R. McGregor*, D.J. Galloway, B.A. Sugden*, A Munro†, G. Bell‡, W.D. George, *University Department of Surgery, Western Infirmary, Glasgow, *Crosshouse Hospital, Kilmarnock, †Raigmore Hospital, Inverness, ‡Inverclyde Royal Infirmary, Greenock, UK*

Despite the widespread use of both suturing and stapling techniques, few studies have scientifically compared them. We report a prospective randomized study of 174 colorectal anastomoses designed to compare sutured (single layer, interrupted polyamide, group A, $n=91$) with stapled cases (EEA® circular stapler, US Surgical Corporation and Autosuture UK, Ascot UK; group B, $n=83$). The mean age was 65·6 years in group A and 67·3 years in group B while the proportion with colorectal cancer was 74 per cent and 72 per cent respectively Numerous pre- and perioperative data were collected including anastomosis and total operating times. Postoperatively a modified sepsis score was monitored and an assessment of anastomotic integrity made, including contrast radiology in 85 per cent of cases.

The anastomosis and operating times along with leak rates are shown in the *Table* There were six perioperative deaths. None of the five in group A resulted from anastomotic complications, unlike the death in group B

We conclude that the use of circular staplers for colorectal anastomoses significantly reduces anastomosis and operating times. Otherwise the results were comparable to those achieved with conventional suturing

	Group A	Group B	P
Anastomosis time min	33 0	21 8	<0 001*
(s e.m.)	(+1·48)	(+1·3*)	
Operating time: min	142 1	127·2	<0 05*
(s.e.m)	(+4 89)	(+4 77)	
Radiological leaks (%)	10 (11%)	4 (4 8%)	0 09†
Clinical leaks (%)	5 (5·5%)	6 (7·2%)	0 64†

* Student's t test, 172 d f, † χ^2 analysis

An evaluation of the safety of piezoelectric lithotripsy in a guinea-pig gallbladder model

A. Darzi, I.M. Reid, E. Kay, J.R.T. Monson, W.A. Tanner and F.B.V. Keane, *Department of Surgery, The Meath and Adelaide Hospitals, Dublin, Ireland*

Controversy surrounds the capacity of extracorporeal shock-wave lithotripsy to cause soft-tissue injury. To address this question, we subjected four groups of guinea-pigs to shock waves. The animals were subjected to different dosages and were killed at different intervals to determine the immediate or delayed effects of increasing the number of shock waves. Macroscopic and microscopic injury to the gallbladder and the neighbouring structures was quantified. Macroscopic changes included haematomata of the gallbladder or neighbouring organs, while the microscopic changes were intramural haemorrhage, eosinophilic infiltrate, small vessel damage and mucosal disruption. Animals were designated as injured or non-injured based on the presence or absence of the above features.

Group	Shock waves	Time of killing	No. of animals injured	%
Group 1	6000	24 h	2	8
Group 2	24 000	24 h	3	33
Group 3a	48 000	24 h	12	100
Group 3b	48 000	2 weeks	2	25
Group 3c	48 000	1 month	0	0
Group 4	6 × 6000 over 6/52	1 week after the last treatment	1	12

The percentage injury was significantly higher in the high-dose lithotripsy (group 3a *versus* group 1, $P<0·001$) and, although these injuries were reversible (group 3b and 3c), it seems that treatment with 6000 piezoelectric shock waves is associated with the least injury and could be administered safely at weekly intervals to a total of 36 000 shock waves.

Prophylactic combination chemotherapy is more effective in preventing peritoneal hydatid cyst development than either albendazole or praziquantel alone following spillage of live protoscolices of Echinococcus granulosus

D.H. Taylor and D.L. Morris, *Department of Surgery, University Hospital, Nottingham, UK*

Recurrence is an important problem after an operation for hydatid disease in man, occurring in as many as 10 per cent of patients.

Thirty-nine gerbils received an intraperitoneal injection of approximately 4000 protoscolices of *Echinococcus granulosus* to simulate surgical spillage. Nine of these gerbils acted as untreated infected controls. The remaining 30 received chemotherapy by daily gavage for 1 month starting on the day of infection: 10 received albendazole (50 mg kg^{-1} day^{-1}), 10 received praziquantel (500 mg kg^{-1} day^{-1}), and 10 received a combination of the two drugs. Eight months after inoculation the gerbils were killed. The number of cysts in each gerbil was recorded.

All chemotherapy significantly reduced ($P<0·01$) cyst numbers. With albendazole, the cysts recorded totalled 22·6 ± 10 per gerbil, with praziquantel 5·9 ± 1·09 and with combination chemotherapy 0·8 ± 0·29, these compared with control figures of 67·6 ± 12·8 per gerbil. Combination chemotherapy was significantly more effective than either of the two drugs given alone ($P<0·001$).

A prospective randomized controlled clinical trial comparing somatostatin and injection sclerotherapy in the control of acute variceal haemorrhage: a preliminary report

S.A. Jenkins, S. Ellenbogen, J.N. Baxter, I. Gilmore, A. Morris and R. Shields, *University Departments of Surgery and Medicine, Royal Liverpool Hospital, Liverpool, UK*

Recent studies have suggested that somatostatin (SRIF) may be of value in the control of bleeding from oesophageal varices. However, in view of the efficacy of injection sclerotherapy in controlling variceal bleeding, it has been suggested that this treatment should be the 'gold standard' against which new therapies are evaluated. Therefore, the aim of this study was to compare the efficacy of SRIF with emergency injection sclerotherapy in the control of acute variceal haemorrhage.

Forty-three consecutive patients admitted with endoscopically proved, severe, bleeding oesophageal varices were randomized to either emergency injection sclerotherapy or SRIF (bolus dose of 250 μg followed by a continuous infusion of 250 μg h^{-1} for 5 days). The aetiology of the accompanying portal hypertension was similar in the two groups as was the distribution of the patients among the categories of Child's classification.

Twenty-two patients received SRIF and 21 injection sclerotherapy. The initial variceal haemorrhage was controlled in all 22 patients receiving SRIF but three bled during the 5-day trial period. Overall control of bleeding was achieved in 19 of the 21 patients randomized to injection sclerotherapy. There was no significant difference ($P=0·52$, Fisher's exact test) between the two forms of treatment.

The initial results of this trial suggest that SRIF is as effective as injection sclerotherapy in controlling acute variceal haemorrhage.

Evaluation of the role of endoscopic sphincterotomy in the treatment of sphincter of Oddi dysfunction

G.M. Fullarton and W.R. Murray, *University Department of Surgery, Western Infirmary, Glasgow, UK*

Postcholecystectomy pain due to sphincter of Oddi dysfunction remains a difficult condition to treat although endoscopic sphincterotomy has been recommended for those patients with confirmed sphincter of Oddi motor abnormalities. We have studied patients with sphincter dysfunction to evaluate the effects of sphincterotomy on their clinical response and on previously reported scintigraphic findings to determine the efficacy of this treatment.

Nine postcholecystectomy patients (two men, seven women, median age 59 years) with clinical and manometric evidence of sphincter dysfunction underwent sphincterotomy for persisting biliary-type pain. Each patient had scintigraphy before and 8 weeks after operation. The patients' clinical response was independently assessed at 3-monthly intervals following sphincterotomy. Scintigraphic analysis demonstrated that the time in minutes to reach maximum counts was significantly reduced from 26·1 ± 1·9 (mean ± s.e.m.) before sphincterotomy to 17·9 ± 1·5 after it ($P<0·01$). Seven out of 9 (78 per cent) patients with dysfunction had a significant improvement in their symptoms after a mean follow-up period of 12 months (range 6–19) although only 6 out of 9 were totally free of pain. These results suggest that endoscopic sphincterotomy in manometrically confirmed dysfunction of the sphincter of Oddi improves bile drainage as measured by quantitative cholescintigraphy and produces at least short-term relief of symptoms.

Does APACHE-II help to predict severity of acute pancreatitis? A prospective comparison with other prognostic systems

M. Larvin and M.J. McMahon, *University Department of Surgery, The General Infirmary, Leeds, UK*

Death from acute pancreatitis results from fulminant major-organ failure early in the attack, or more commonly from late septic complications of pancreatic necrosis. Prediction of organ failure and necrosis is important for evaluation of medical and surgical treatments, and as an aid to management. Existing multiple criteria systems (Ranson, Imrie) measure initial severity, and cannot predict pancreatic necrosis. Acute Physiology/Chronic Health Enquiry (APACHE-II) scores[1] allow initial assessment and sequential monitoring of major-organ failure and sepsis.

A prospective evaluation of APACHE-II scores was undertaken in 290 attacks of acute pancreatitis. By predefined criteria, complications were classified as early major-organ failure (within first week) ($n=24$) and pancreatic necrosis, proved at autopsy or laparotomy ($n=15$). Data were collected to calculate Ranson, Imrie and daily APACHE-II scores.

		Complications			
		Multi-organ failure		Pancreatic necrosis	
Time (h)	System and cut-off level	Sensitivity	PPV (%)	Sensitivity	PPV (%)
0	APACHE-II > 10	83·3	32·3	80·0	19·4
24	APACHE-II > 9	87·5	33·3	86·7	20·6
48	APACHE-II > 8	91·7	35·5	86·7	21·0
48	Ranson > 2	83·3	16·7	80·0	10·0
48	Imrie > 2	66·7	26·2	66·7	16·4
72	APACHE-II > 8	91·7	36·2	86·7	21·3
96	APACHE-II > 8	91·7	39·3	93·3	24·6

PPV, positive predictive value.

Admission APACHE-II scores provided similar accuracy to Ranson and Imrie scores at 48 h for identifying severe attacks. Ranson and Imrie scores proved poor at predicting necrosis compared with APACHE-II scores, which could detect necrosis and necrosis plus organ failure with increasing accuracy after 3 days. The APACHE-II system has the potential to identify severe attacks, providing more rapid stratification of patients for entry into clinical trials, and sequential APACHE-II scores may give early warning to clinicians of pancreatic necrosis.

1 Knaus WA, Draper EA, Wagner DP *et al* APACHE-II a severity of disease classification. *Crit Care Med* 1985; **13** 818–29

Oxygen free radical-dependent and radical-independent release of gut peptides in intestinal ischaemia

L. Meleagros, R.A. Spokes, J. Domin, M.A. Ghatei and S R. Bloom (introduced by R.C.N. Williamson), *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK*

Ischaemia and reperfusion causes intestinal injury by at least two, possibly linked, mechanisms: oxygen free radical (oxy-radical) generation and activation of the enzyme phospholipase A_2 (PLA_2) By inhibition of oxy-radical generation with allopurinol and of PLA_2 with quinacrine, an investigation was made of their role in the release of the gut peptides vasoactive intestinal polypeptide (VIP), β-calcitonin gene-related peptide (β-CGRP), peptide YY (PYY); somatostatin (Som) and enteroglucagon (EG) from reperfused ischaemic intestine Three groups (B, C, D, $n=6$ per group) of anaesthetized male Wistar rats were subjected to superior mesenteric artery (SMA) occlusion for 20 min followed by reperfusion for 20 min. Animals in group B were untreated. Group C received allopurinol 50 mg kg^{-1} day^{-1} orally for 3 days and 50 mg kg^{-1} intravenously; and group D received quinacrine 10 mg kg^{-1} intravenously before SMA occlusion. Control animals ($n=6$, group A) had sham SMA occlusions Arterial blood samples were taken after reperfusion and plasma peptides were measured with specific radioimmunoassays. Results (mean ± s.e.m. fmol/ml), analysed by ANOVA, are shown below.

Group	VIP	β-CGRP	PYY	Som	EG
A	3±0·6	15±3	9±2	21±7	38±1
B	28±3***	37±7*	37±6***	61±8**	135±11***
C	32±6***	18±4†	36±6***	30±6‡	65±10*†
D	30±4***	21±4	37±8***	38±8	103±22**

* $P<0{\cdot}05$, ** $P<0{\cdot}005$, *** $P<0{\cdot}001$ (*versus* control); † $P<0{\cdot}05$, ‡ $P<0{\cdot}01$ (*versus* no treatment)

These findings demonstrate that injury mediated by the oxy-radical causes the release of β-CGRP, Som and EG but not VIP and PYY. PLA_2 activation is not a major mechanism of peptide release Therefore, measurement of plasma levels of gut peptides can differentiate between those that are dependent or independent of the oxy-radical and PLA_2-induced intestinal ischaemia/reperfusion injury

In vivo comparison of proglumide and CR-1409 inhibition of cholecystokinin-induced changes in the biliary tract of the guinea-pig

G.J. Poston and J.C. Thompson, *Department of Surgery, UTMB, Galveston, Texas, USA*

The purpose of this study was to compare the effects of two cholecystokinin (CCK) antagonists, proglumide and CR-1409, on CCK-induced changes in intrabiliary pressure *in vivo* We have substantially modified the constant infusion biliary manometry model, successfully used in large animals, to measure gallbladder contractility in guinea-pigs A silicone manometry catheter was placed in the gallbladder fundus of an anaesthetized guinea-pig, and the biliary tree was constantly infused at 0·1 ml/min with saline The intraluminal pressure of the system was continuously recorded The model was used to demonstrate a dose-response curve to bolus administration of exogenous CCK (from 0·01 to 1·0 nmol/kg), and also to study the actions of proglumide, a specific antagonist to gastrin and cholecystokinin (CCK), and CR-1409, a newer CCK antagonist, on CCK-induced contraction of the guinea-pig gallbladder *in vivo*. Proglumide at a dose of 5 mmol/kg completely abolished increases in intrabiliary pressure caused by CCK (0·5 nmol/kg), whereas this effect was achieved by only 5 μmol/kg of CR-1409. In both cases there was full recovery from CCK antagonism within 1 h CR-1409 is thus 1000 times more potent than proglumide against CCK-induced changes in intrabiliary pressure *in vivo*, and appears to be a useful pharmacological reagent to study CCK-mediated components of physiological contraction of the gallbladder

The effects of vasoactive drugs on the collateral circulation of rats with portal hypertension

S.A Jenkins, J. Yates, D.M. Nott, S. Ellenbogen, T. Cooke and R. Shields, *University Department of Surgery, Royal Liverpool Hospital, Liverpool, UK*

It is generally assumed that control of variceal bleeding by vasoactive drugs results from a reduction in collateral bloodflow secondary to splanchnic vasoconstriction and a reduction in portal pressure, a hypothesis which has never been validated directly. The aim of this study was to investigate the effects of vasoactive drugs on collateral bloodflow and portal pressure simultaneously in rats with portal hypertension

Rats with portal hypertension (partial portal vein ligation) received intravenous bolus doses of 2 μg somatostatin (SRIF), 2 μg SMS 201-995, 0·4 i.u. vasopressin or the same volume of isotonic saline over 30 s Arterial blood pressure and portal pressure (PP) were recorded continuously whilst collateral bloodflow was measured before and after the administration of drugs or saline, by consecutive intrasplenic injection of a non-diffusable marker, ^{99}Tc-methylene diphosphonate and ^{99m}Tc-albumin microspheres

Vasopressin elicited the greatest reduction in portal pressure (from 13·00±0·71 to 6·88±0·75 mmHg; $P<0{\cdot}001$ Student's paired *t* test) but had no significant effect on collateral bloodflow. Both SRIF and SMS 201-995 also significantly reduced portal pressure but to a lesser degree than vasopressin However, both SRIF and SMS 201-995 significantly reduced collateral bloodflow (SRIF from 26·83±4·42 to 11·33±1·79 per cent, SMS 201-995, from 36·25±6·93 to 20·88±6·4 per cent, $P<0{\cdot}001$).

These results indicate that SRIF and SMS 201-995, although having a less marked effect than vasopressin on portal pressure, produce a much greater effect on collateral bloodflow which may partly explain their greater efficacy in controlling acute variceal bleeding.

Converted striated muscle neosphincter: a canine model

R.I. Hallan, N.S. Williams, M.A. Pilot, M.F. Grahn, T H. Koeze* and E.S. Watkins*, *Surgical and *Neurosurgical Units, The London Hospital, London, UK*

The outcome of the gracilis sling procedure for faecal incontinence is often unsatisfactory as the sphincter is adynamic. Electrical stimulation of the muscle might result in adequate and appropriate sphincter contraction To investigate this an electrically controlled sphincter model was created in six dogs The sartorius muscle was mobilized on its neurovascular pedicle into the abdominal cavity to form a sphincter around a Thiry–Vella loop. Electrodes connected to an external stimulator were sutured close to the nerve supplying the muscle The sphincter was able to reduce or stop the flow of water through the Thiry–Vella loop, but only for a short period of time due to muscle fatigue. To overcome this, chronic low-frequency stimulation (CLFS) from an implanted stimulator was used to convert the fatiguable, fast-twitch muscle to a fatigue-resistant, slow-twitch muscle. After 6 weeks there was a significant change in the tetanic fusion frequency, the time from stimulus to peak tension recorded by a strain gauge, and muscle enzyme activities The successful conversion resulted in a significant prolongation of sphincter competence

	Fusion frequency	Time from stimulus to peak tension	Time sphincter remains competent
Before CLFS	20 (2) Hz	63 (7) ms	1·5 (0·9) min
After CLFS	12 (2) Hz	187 (11) ms	6·3 (2·3) min
Paired *t* test	$P=0{\cdot}01$	$P=0{\cdot}002$	$P<0{\cdot}05$

Data are all means (s.e.m.)

The electrically stimulated sartorius neosphincter functions well in the dog This technique should improve the gracilis sling procedure when used to treat faecal incontinence and is currently being evaluated in humans

Home assessment of anorectal motility and external sphincter EMG in idiopathic faecal incontinence

D. Kumar, D Waldron and N S. Williams, *Surgical and Gastrointestinal Science Research Units, London Hospital Medical College, London, UK*

Patients with idiopathic faecal incontinence are conventionally assessed in a laboratory setting for a short period of time These studies have led to the belief that impairment of external anal sphincter is the main aetiological factor

To evaluate the role of internal and external sphincters in idiopathic faecal incontinence, we studied six subjects with incontinence and 14 healthy controls for a mean duration of 21 0 and 20 3 h per subject respectively. Pressure was recorded by a two-channel Gaeltec probe with sensors positioned in the rectum and mid-anal canal respectively. External sphincter EMG activity was recorded by surface electrodes applied 0 5 cm from the anal verge All subjects ate normal meals and slept at home Patients with faecal incontinence showed more (*P* <0 01) episodes of anal relaxation the mean ± s.e m. was 11 6 ± 1 8 h^{-1} *versus* healthy controls 7 4 ± 2 0 h^{-1} Their duration of anal relaxation was significantly longer than in healthy controls (48 ± 3·1 s *versus* 28 4 ± 3 9 s, *P* <0 001) External sphincter EMG activity in the two groups was not statistically different: incontinent patients had 14·2 ± 2·8 action potentials per 10 min while controls had 12 8 ± 3·2. Our data show that anal relaxation occurs more frequently and for a prolonged period of time in patients with idiopathic faecal incontinence; the external anal sphincter does not appear to be affected We conclude that the incontinence is the result of internal anal sphincter dysfunction rather than the external sphincter as is more generally believed.

Does anal sphincter function improve following restorative proctocolectomy?

W.A Kmiot, M. Pinho, K. Yoshioka and M R.B. Keighley, *The General Hospital, Birmingham, UK*

In order to determine the influence of time on anal sphincter pressures following restorative proctocolectomy, 10 patients had anal pressures measured preoperatively and at 3, 6 and 12 months after operation. A closed rigid 5-mm diameter catheter with a 1-cm water-filled balloon was used to measure anal pressure at 1-cm intervals along the anal canal A further 12 patients had similar measurements 18 and 24 months after operation. The median age was 28 years (range 18–44 years) All ileo-anal anastomoses had been hand sutured and all mucosectomies performed from above; pouch design was J ($n=12$) or W ($n=10$). Maximum resting anal pressures were lower at 3 months (median 80 (range 50–100), *P* <0 03, Wilcoxon matched pairs test), 6 months (90 (50–150); *P* <0 01) and 12 months (100 (70–135)) postoperatively than before operation (110(70–160)) Furthermore, the resting pressure at 24 months (105 (50–160)) was higher than at 18 months (100(50–150), *P* <0 05). Maximum squeeze anal pressures were lower at 3 months (185 (150–230), *P* <0 03) and 6 months (200 (150–300), *P* <0 01) postoperatively than before operation (250 (190–300)) However, this difference was not significant at 12, 18 and 24 months Patients with preoperative resting anal pressures lower than the median of 110 cmH_2O had a greater number of soiling episodes postoperatively than the remainder (3·5/24 h *versus* 1 2/24h)

Resting anal pressure improves after restorative proctocolectomy and probably accounts for decreasing soiling episodes with increasing time after operation

Anal continence depends on sphincter recruitment by stress rather than absolute sphincter strength

N.R Womack, J F.B. Morrison* and N.S Williams, *Surgical Unit, The London Hospital, London and *The Department of Physiology, The University of Leeds, Leeds, UK*

Neurogenic weakness of the external anal sphincter is implicated in the aetiology of idiopathic faecal incontinence yet only some patients with such weakness develop incontinence To investigate why this is so EMG activity of the sphincter was recorded in three groups, each comprising 25 women and five men. control subjects (mean age 59 ± s.e.m 2 7), continent patients (aged 51 ± 2 8) and incontinent patients (aged 65 ± 1 9, *P* <0 001 compared with continent patients); the patients had a similar degree of sphincter weakness on manometric and fibre-density testing. Recordings were made whilst continence was threatened in two ways first, rectal distension was simulated by balloon distension to maximal tolerable volume; and secondly, intra-abdominal pressure was raised by a series of forced expirations.

Sphincter behaviour in the study groups was significantly different in both situations. Rectal distension to maximal tolerable volume produced sphincter inhibition to levels of activity below those present at rest in 44 per cent of controls, 28 per cent continent patients, and 72 per cent of incontinent patients (*P* <0 01 compared with continent) The rise in intra-abdominal pressure necessary to cause sphincter recruitment was raised in both study groups, with the impairment significantly greater in the incontinent patients then in the continent patients (controls 0 8 ± 0·4 cmH_2O, continent 3 3 ± 0 7, *P* <0 002 compared with controls, incontinent 7 0 ± 1 1, *P* <0 001 compared with controls, *P* <0 002 compared with continent).

These results imply that in the clinical situation the manner in which the external anal sphincter responds when continence is threatened may be more important than sphincter strength *per se* in determining whether continence is maintained

Five-year follow-up of changes in pelvic floor innervation after childbirth

S J. Snooks, M M. Henry and M Swash, *St Bartholomew's and St. Mark's Hospitals, London, UK*

Fourteen multipara of mean age 31 5 (range 29–34 years) were studied employing the techniques of single-fibre electromyography (SFEMG), transrectal pudendal nerve stimulation, anorectal manometry and assessment of perineal descent Each woman was studied at 3 months before delivery, and at 48 h, 2 months and 5 years after vaginal delivery These results show that the pudendal nerve terminal motor latency (PNTML) and SFEMG fibre density of the external anal sphincter (EAS) muscle remained significantly increased 5 years after the initial monitored vaginal delivery compared with nulliparous control subjects (*P* <0 01) Perineal descent on straining no longer occurred in 11 women; however, anal canal pressures on voluntary contraction remained significantly low.

Seven women had increased fibre density in the sphincter muscle, five of whom had increased PNTML A further three women had increased PNTML alone, but latency was unilaterally unrecordable in three These multipara therefore had evidence of progressive denervation associated with continuing mechanical weakness of the external sphincter muscle despite, in 11 women, a complete absence of perineal descent.

Five women with increased PNTML and fibre density had stress incontinence of urine, three of whom also had incontinence of flatus These results are consistent with progressive damage to the innervation of the external anal sphincter muscle in multipara after vaginal delivery.

Time	PNTML (ms) Right	PNTML (ms) Left	FD of EAS	Voluntary contraction (cmH_2O)	Perineal descent (cm)
Antenatal	—	—	1 42 ± 0 21	73 5 ± 31 1	0 82 ± 0 57
Postnatal					
48 h	2 23 ± 0 29*	2 37 ± 0 67*	—	47 3 ± 13 0*	−1 55 ± 0 50*
2 months	1 97 ± 0 12	1 89 ± 0 22	1 59 ± 0 25*	50 0 ± 30 0*	−1·02 ± 0 48*
5 years	2 25 ± 0 18*	2 3 ± 0 5*	1·82 ± 0 47*	50 0 ± 29 9*	+0 87 ± 0 66
Controls	1 90 ± 0 20	2 0 ± 0 20	1 30 ± 0 16	104 7 ± 50 5	+0 08 ± 0 70

* *P* <0 01 significant difference from controls (Wilcoxon's rank sum test)
(−) denotes distance of perineum beneath plane of ischial tuberosities
Results are mean ± s d

Does psychological and pain stress affect anorectal motility and external sphincter activity in humans?

D. Kumar, D Waldron, D L. Wingate and N S. Williams, *Surgical and Gastrointestinal Science Research Units, London Hospital Medical College, London, UK*

To evaluate the effect of psychological and pain stress on the human anorectum and external sphincter, we studied six healthy subjects (three men and three women, age range 20–55 years) Anorectal motility was measured using a Gaeltec probe with sensors located in the mid-anal canal and rectum External sphincter EMG activity was recorded by surface electrodes Psychological stress was applied by requiring the subject to play a competitive video game for 30 min, and pain stress applied by immersing the hand in ice-cold water for 30 min, these two forms of stress were separated by a rest period of 30 min. Anorectal motility and external sphincter EMG for the two stress periods were compared with those under unstressed conditions but in the same posture. There was a rise of 10 ± 3·8 mmHg in the anal canal pressures during the two stress periods Intermittent phasic contractions, seen in the rectum and anal canal, were virtually abolished in all subjects during both stress periods Normal external sphincter EMG activity (11 ± 1·9 action potentials per 30 min) was reduced to 4 ± 1·3 under stress (*P* <0 01) Our data show that both psychological and pain stress inhibit rectal motility and external sphincter activity but produce a sustained tonic rise in anal canal pressure, reflecting an increased tone in the internal anal sphincter.

'Total pelvic floor' repair is superior to conventional postanal repair for faecal incontinence

M. Pinho, K. Yoshioka and M.R.B. Keighley, *The General Hospital, Birmingham, UK*

Postanal repair is often associated with poor results Since postanal repair does not correct the deficient anorectal angle and as there is preoperative evidence of anterior pelvic floor weakness in many patients' with incontinence, we have added an anterior levatorplasty and anterior external anal sphincter plication to conventional postanal repair. 'total pelvic floor repair'

Fifteen patients have been prospectively studied before and after total pelvic floor repair using pre- and postoperative manometry and videoproctography. Results have been compared with 15 patients having conventional postanal repair. At a mean follow-up of 6·2 months after total pelvic floor repair, complete continence was recorded in eight (53 per cent), an improvement in five (33 per cent) and no difference in two (13 per cent) By contrast, after postanal repair at the same period of follow-up, complete continence was recorded in only five (33 per cent), improvement in four (27 per cent) and six (40 per cent) were no better. A significant decrease in pelvic floor descent and a lower rest position were found after total pelvic floor repair but there was no difference after postanal repair. Manometric studies found no significant difference after repair in either group Anterior levatorplasty with anterior external sphincter plication was performed in eight postanal repair failures, with improvement of continence recorded in seven.

Prolonged follow-up, as well as an ongoing prospective randomized study, is expected to define the role of total pelvic floor repair in the treatment of idiopathic faecal incontinence

Parameters which will identify patients who are likely to remain incontinent after abdominal rectopexy

K. Yoshioka and M.R.B. Keighley, *The General Hospital, Birmingham, UK*

We have studied 18 incontinent patients with a full-thickness rectal prolapse preoperatively, using anal manometry, saline infusion tests and videoproctography. Continence was restored in only 12 patients Persistent incontinence could not be identified by resting anal pressures (continent patients 57 cmH$_2$O (range 37–80), incontinent 46 cmH$_2$O (21–59)) or by maximum squeeze pressures (continent 84 cmH$_2$O (64–121); incontinent 73 cmH$_2$O (33–94)). The volume of the first leak during saline infusion was significantly lower in patients who remained incontinent (30 ml (10–40)) compared with those who became continent (80 ml (40–300); $P<0·025$) Median preoperative anorectal angles during maximum pelvic floor contraction were 106° (91–122) in patients whose continence was restored compared with 133° (131–152; $P<0·025$) in those who remained incontinent. Pelvic floor descent during straining was also significantly greater in patients who remained incontinent (4·8 cm (3·8–6·8)) compared with those who became continent (2·0 cm (0·9–4·3), $P<0·005$). The anal canal was shorter in the patients who remained incontinent (2·3 cm (1·2–3·1)) compared with the remainder (3·7 cm (3·6–6·2), $P<0·05$).

Using these criteria, it might be possible to select patients in whom postanal repair should be performed synchronously with abdominal rectopexy

The effect of photodynamic therapy on skeletal muscle and tumours using five different photosensitizers

E.B. Chevretton, M.C. Berenbaum*, R. Bonnett† and N.S Williams, *Department of ENT Surgery and the Surgical Unit, The London Hospital, *Department of Experimental Pathology, St Mary's Hospital Medical School, and †Department of Chemistry, Queen Mary College, London, UK*

Treatment of head and neck cancer poses special problems as the close proximity of structures in this region means that normal tissues may be damaged Exposure of photosensitized muscle to light causes rapid oedema and, if the damage is severe, necrosis Five photosensitizers, haematoporphyrin derivative (HpD), Photofrin II and the three isomers of the tetrahydroxyphenylporphyrins (*meta-*, *ortho-* and *para*-THPP), were compared for their ability to sensitize skeletal muscle and tumours BALB/c mice were given various doses of sensitizers Twenty-four hours later the posterior aspect of one lower leg was exposed to 10 J cm^{-2} of light of an appropriate wavelength from a copper vapour-pumped dye laser. Muscle damage was measured as percentage weight increase due to oedema at 4 h and percentage area necrosis at 48 h These results were compared with those obtained for depth of tumour necrosis in subcutaneous PC6 tumours in mice[1].

The THPPs were more potent than HpD and Photofrin II in causing both tumour necrosis and muscle damage. The table below is a cost–benefit analysis comparing the different photosensitizers in terms of muscle swelling and necrosis obtained for a given depth of tumour necrosis *m*-THPP produces significantly less muscle damage than HpD and Photofrin II for 3 and 4 mm of tumour necrosis and would be the sensitizer of choice in photodynamic therapy where muscle was liable to damage

	Percentage muscle swelling for 1–4 mm of tumour necrosis				Percentage muscle necrosis for 1–4 mm of tumour necrosis			
Sensitizer	1	2	3	4	1	2	3	4
m-THPP	6	7	9	10	18	22	30	48
o-THPP	6	12	18	26	nd	nd	nd	nd
p-THPP	7	9	20	26	12	40	77	91
HpD	18	35	46	46	33	55	>68	
'Photofrin II	10	44	>36		20	55	86	>86

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Inhibition of RT112 human transitional tumour xenografts by stearic and sterculic acids

B. Fermor, N.A. Habib, S.B. Kelly, C.B. Wood* and R.C.N. Williamson*, *Departments of Surgery, Bristol Royal Infirmary and *Royal Postgraduate Medical School, London, UK*

Oleic acid increases the growth of normal and malignant cells, stearic acid inhibits cell growth[1]. Saturated stearic acid is desaturated to mono-unsaturated oleic acid by the enzyme complex Δ^9-desaturase Sterculic acid, a cyclopropene fatty acid, inhibits the activity of this enzyme[2].

Male athymic MF1 nude mice received 5×10^6 RT112 tumour cells subcutaneously ($n=24$) and were randomly allocated to two equal groups Group I received 4 mg/ml stearic acid plus 2 mg/ml sterculic acid dissolved in 0·2 ml liquid paraffin subcutaneously twice weekly, group II (controls) received 0·4 ml liquid paraffin subcutaneously twice weekly

	Mean tumour volume (mm^3 ± s e m.)	
Day	Stearic + sterculic	Paraffin
13	10·2 ± 6·8	9·5 ± 4·2
22	48·7 ± 20·0	84·1 ± 19·6
34	147·0 ± 51·5	306·4 ± 100·1
42	164·2 ± 44·6*	495·9 ± 136·8

Significance *versus* controls $^*P=0·03$

Forty-two days after implantation of tumour cells, stearic and sterculic acids induced a significant reduction (66·9 per cent) in mean tumour volume compared with control animals ($P<0·05$) These data show the ability of stearic acid in combination with sterculic acid to significantly inhibit tumour growth *in vivo*.

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2. Jeffcoat R. Studies on the inhibition of the desaturases by cyclopropenoid fatty acids. *Lipids* 1976; **12**. 480–5

Is the laser really necessary for successful photodynamic therapy?

M. Turkish, P. Durdey, M.F. Grahn, L. Ilincic, J.T. Allardice and N.S. Williams, *The Surgical Unit, The London Hospital, London, UK*

Photodynamic therapy is receiving increasing attention as a treatment for malignant disease However, the cost and maintenance of lasers is prohibitive and this may restrict its use in patients who are otherwise suitable.

We have therefore investigated alternative non-coherent light sources to determine whether a comparable cytotoxic effect can be achieved over similar time periods and irradiation doses. Red and green laser light were compared with theatre lights and daylight tungsten lamps. Multicellular tumour spheroids from the cell line HRT18 were pretreated with 10 μg/ml of haematoporphyrin derivative, and the cytotoxic effect of different light sources was measured using tritiated thymidine incorporation. Results are expressed as mean (±s e m) percentage inhibition.

Light source	Irradiance ($J\ cm^{-2}$)	Inhibition (%)
Red laser light	10 J/cm^2	54·7 (±6)*†
Green laser light	10	35·5 (±7)
Theatre lights	10	87·0 (±3·7)*
Tungsten daylight lamps	4·25	70·4 (±6·1)†

*,† $P<0·01$ by analysis of variance

For a given irradiance, growth inhibition of multicellular tumour spheroids was significantly greater with a polychromatic light source (theatre lights and tungsten daylight lamps) than laser light. Polychromatic light may not achieve as effective tissue penetration as does red light. However, for the ablation of superficial tumours and adjuvant treatment of the tumour bed peroperatively, the cheaper alternative of an adapted polychromatic light source (tungsten daylight lamps) may allow more widespread use in clinical practice.

Urokinase promotes the growth of a murine tumour in vivo

G.T. Layer and K.G Burnand, *Department of Surgery, St. Thomas' Hospital Medical School, London, UK*

Urokinase receptors are described on the plasma membrane of breast cancer[1] and murine melanoma cells[2] It is postulated that autocrine secretion of plasminogen-activating enzyme urokinase determines normal cellular growth and that malignant transformation is due to an excess of urokinase

The effects of intraperitoneal urokinase, intramuscular stanozolol (which affects tissue-type plasminogen activator levels) and oral aminocaproic acid (ε-ACA) on systemic and lung and kidney tissue fibrinolytic activity in groups of ten C57Black mice were investigated These drugs were also administered to mice inoculated subcutaneously with Lewis lung carcinoma to determine whether exogenous urokinase or drugs altering fibrinolysis affect tumour growth

Significant differences in systemic activity measured by euglobulin clot lysis (ECLT) were detected between all groups No differences in tissue activity were found

Table 1

		Urokinase	Stanozolol	ε-ACA	Controls
ECLT (min)	median	70	215	15·5	28
	range	35–120	120–280	11–35	16–50
$\frac{10^6}{(ECLT)^2}$	mean	270	37	4934	1589

One way analysis of variance $F=16·1$, $P<0·01$

There was a significant increase in the primary tumour weights arising for urokinase and stanozolol treated groups compared with controls. Pulmonary metastases were also increased by urokinase

Table 2

Weight (g)	Urokinase	Stanozolol	ε-ACA	Controls
Primary tumour	2·53±0·33*	2·57±0·33*	1·18±0·21	1·15±0·14
Metastases	27·9±6·3†	27·0±9·1	20·3±4·0	14·5±3·7

Data are means±s.e m., * $P<0·004$, † $P<0·043$, *versus* controls (Mann–Whitney U tests)

It is concluded that urokinase-type plasminogen activator promotes growth of Lewis lung carcinoma *in vivo* Its effect is similar to stanozolol and may be mediated by urokinase receptors, causing direct cellular changes or an effect on tumour-associated fibrin This provides further support for a role for plasminogen activators and fibrinolysis in malignancy

1 Needham GK, Sherbet GV, Farndon JR, Harris AL Binding of urokinase to specific receptor sites on human breast cancer membranes *Br J Cancer* 1987; **55**: 13–6

2 Hearing VJ, Law LW, Corti A, Appella E, Blasi F. Modulation of metastatic potential by cell surface urokinase of murine melanoma cells. *Cancer Res* 1988; **48**· 1270–8

Tumour-cell DNA content in squamous carcinoma of the head and neck: prediction of response to chemotherapy

L.D. Cooke, T G. Cooke, G. Forster, T.R. Helliwell, D. Spiller and P.M. Stell, *Departments of Otorhinolaryngology, Surgery, Pathology and Radiation Biology, University of Liverpool, UK*

In two phase III trials we have shown that cisplatinum significantly prolongs survival in patients with end-stage squamous carcinomas of the head and neck region[1]. Factors such as performance status, age, site, nodal status, and serum albumin are prognostic factors but are not significantly clear-cut to define which patient should be treated In an attempt to improve on this we have measured tumour cellular DNA in this sample group

We studied tumours from 41 untreated patients and 52 patients receiving cisplatinum as part of a prospectively randomized trial Sections of tumour of 50 μm thickness were enzymatically disaggregated, treated with RNAase, and the DNA stained with propidium iodide Following analysis by flow cytometry they were classified as diploid or aneuploid

Fifty-four per cent of all tumours were aneuploid and 46 per cent diploid, with similar proportions in both treated (57.43 per cent) and untreated patients (51·49 per cent) Survival time with diploid tumours increased from 68 days for untreated patients to 128 days after chemotherapy, but this difference was not significant ($\chi^2=1·91$) However, the survival of patients with aneuploid tumours increased fourfold from 55 to 224 days ($\chi^2=10·29$, $P<0·001$)

This study suggests that cisplatinum chemotherapy in end-stage head and neck cancer should be restricted to patients with aneuploid tumours

1 Campbell JB, Dorman EB, Helliwell TR, *et al* Factors predicting response of end-stage squamous cell carcinoma of the head and neck to cisplatinum *Clin Otolaryngol* 1987; **12**, 167–176

Are there oestrogen receptors in pancreatic carcinoma?

O.M. Taylor , J Harrison†, P.N. Cowen*, M.J. McMahon and E.A. Benson; *Departments of Surgery and *Histopathology, General Infirmary, Leeds, and †Queens Medical Centre, Nottingham, UK*

Recent reports have suggested the presence of oestrogen receptors in pancreatic carcinomas If true, there is the potential for treatment by hormone-manipulation techniques, there have been suggestions of benefit in patients treated with tamoxifen[1].

Biopsies of human pancreatic adenocarcinoma were examined for the presence of receptors to oestradiol, using three techniques. (1) iso-electric focusing (IEF); (2) ERICA, using a monoclonal antibody to oestrophilin (the oestrogen receptor protein), and (3) ERD-5, using a monoclonal antibody to a cytoplasmic oestrogen receptor-associated protein A slice of tissue demonstrated histologically to contain tumour was tested in each case

Twenty-five biopsies were assayed with ERICA, 13 with ERD-5, and nine by IEF Using ERICA and IEF all were negative for oestrogen receptors Using the ERD-5 all were positive, as well as two biopsies containing normal pancreas

Pancreatic carcinoma tissue has been reported to contain oestrogen receptors, detected using biochemical assays[2] We were unable to demonstrate receptors with IEF, or with the more sensitive ERICA ERD-5 has been reported to correlate poorly with other assays of oestrogen receptors in breast tissue

These results suggest that oestrogen receptors are not present in pancreatic carcinoma, or that the receptor present is of a different type to that found in breast and uterine tissue. Failure to demonstrate a specific oestradiol receptor suggests that a clinical response to tamoxifen is unlikely

1 Theve NO, Pousette A, Carlstrom K Adenocarcinoma of the pancreas—a hormone sensitive tumour? A preliminary report on Nolvadex treatment. *Clin Oncol* 1983, **9**· 193–7

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Metastatic tumour growth in the regenerating liver

M. Loizidou, A. Cooper, R. Lawrence, P. Alexander and I. Taylor, *University Surgical Unit, Southampton, UK*

Metastatic growth occurs preferentially at sites of trauma , e.g healing wounds, anastomoses[1] and damaged liver[2]. We have studied the role of parenchymal liver regeneration on the growth of tumour cells delivered intraportally

In control rats, 2×10^5 intraportally injected syngeneic MC28 sarcoma cells gave rise to minimal tumour in the liver (<2 superficial foci in 10/25 rats). If these cells were injected from 15 min to 2 days after partial (two thirds) hepatectomy, tumour grew in all cases (n=40), almost invariably at the resection site Stimulation of DNA synthesis, as measured by uptake of [^{3}H]thymidine, was effectively complete by 4 days When MC28 cells were injected 5–7 days after hepatectomy, tumour did not grow at the resection site, many foci appeared not only superficially but also predominantly within the regenerated lobe (>20 foci in 30/30 rats) Cells injected 10 days after hepatectomy yielded levels of tumour foci similar to the control.

We conclude that promotion of tumour growth in partially hepatectomized rat livers is caused by at least two mechanisms, one related to trauma and the other to a delayed effect of regeneration

1. Skipper D, Jeffrey MJ, Cooper AJ *et al*. Preferential growth of bloodborne cancer cells in colonic anastomoses *Br J Cancer* 1988; **57**: 564–8
2. Fisher B, Fisher ER Trauma and the localisation of tumour cells. *Cancer* 1967; **20**. 23–31

The effect of a gastrin receptor antagonist on the growth of gastrin-responsive primary human colorectal tumours

S.A. Watson, L.G. Durrant, R. Chadderton* and D L. Morris*, *Department of Cancer Research, Nottingham University, and *Department of Surgery, University Hospital, Nottingham, UK*

A series of 40 colorectal human tumours was screened for their growth response to gastrin (assessed by ^{75}[Se]selenomethionine incorporation) Of the colorectal tumours 57·5 per cent responded trophically to the hormone Low numbers of gastrin-binding sites (from 1×10^2 to 1×10^3/cell) could be detected in 50 per cent of all tumours using ^{125}I-labelled gastrin in a radioimmunoassay.

If the growth of human colorectal tumours is gastrin-dependent (possibly autocrine/paracrine) then gastrin receptor antagonists should reduce the growth of such tumours. A potent gastrin receptor antagonist (with the same affinity for the receptor as gastrin) significantly reduced the *in vitro* growth in four of six colorectal tumours (as measured by label incorporation), and reduced the *in vitro* response to gastrin in three of six colorectal tumours Gastrin receptor antagonists may be potential therapeutic agents for treatment of such tumours

Prospective study of 'risk' of gastric cancer in new onset dyspeptic patients, comparing a simple scoring index with a clinician's assessment

E.M. Chisholm, B.J. Unwin, A.G. Morgan and G.R. Giles, *Department of Surgery, St. James's Hospital, Leeds, and Airedale Hospital, Keighley, UK*

To decrease the mortality rate for gastric cancer patients, more cases of potentially curable cancer must be found. A simple scoring index to indicate 'risk' of gastric cancer in a dyspeptic population and therefore to determine priority for endoscopy has been evaluated in a prospective study of 300 consecutive referrals to a dyspepsia clinic over a 2-year period

Each patient answered eight critical gastrointestinal questions, using a previously validated scoring index, the risk of cancer was ascribed as high (probability P>0·05), intermediate, or low (P<0·0018) Unaware of this risk assignment, the clinicians recorded their assessment. All patients underwent gastroscopy and ultrasound examination Mean follow-up was 32 months (range 18–42).

Sixteen patients presented with gastric cancers Fifteen cancers (eight curable) were identified as high risk by the scoring index compared with nine (five curable) cancers defined by the clinician The specificity and positive and negative predictive yields were very similar for both the scoring index and the clinician· 28 per cent of patients were identified as low risk by both assessors and confirmed upon investigation To date no further cancer has arisen in the remaining patients.

A simple risk index for gastric cancer using symptom analysis can predict cancer risk as accurately as a clinician, with a high yield per endoscopy, and may therefore be useful in determining priority for endoscopy to detect potentially curable gastric cancer.

Why is anti-reflux surgery superior to medical treatment for refractory gastro-oesphageal reflux?

S.J Walker, S. Holt, C J. Sanderson and C J. Stoddard, *University Department of Surgery, Royal Liverpool Hospital, Liverpool, UK*

It is unknown why a minority of patients with gastro-oesophageal reflux fail on medical treatment yet have a successful outcome after anti-reflux surgery. In order to investigate this we prospectively studied 16 patients (14 men) mean age 50 years (range 36–73) with prolonged, refractory reflux whilst on medical treatment and continued to study them after anti-reflux surgery. Patients were assessed before treatment by symptom scoring, endoscopy, manometry and ambulatory oesophageal pH monitoring. Symptoms and pH were assessed on treatment with ranitidine 150 mg b.d. alone for 1 week, and again with ranitidine plus metoclopramide 10 mg t.d s. for a further week Reassessment was performed 3 months after transabdominal surgery (Nissen, 9, Lind, 7) Six parameters of reflux were examined at 5 pH levels by 22-h pH monitoring (Ormed) Surgery significantly improved the median results at all pH levels compared with no treatment whilst medical management only improved results at some levels.

Treatment	Upright (%)†	Supine (%)†	Reflux	Reflux 5 min
No treatment	17·1 (8·5, 23·4)	17·4 (8·0, 44·0)	34 (21, 52)	12 (5, 18)
Ranitidine	13·0 (6·5, 20·0)	8·4 (0·1, 18·6)*	34 (21, 42)	19 (1, 12)*
Ranitidine + metoclopramide	8·9 (4·7, 15·2)*	4·9 (1·2, 14·5)*	24 (16, 39)	6 (3, 10)**
3 months after surgery	3·6 (1·2, 9·9)**	1·4 (0·0, 9·0)*	10 (2, 19)**	4 (1, 6)**

*P<0·05, **P<0·01, Wilcoxon signed-rank test at pH 4 †Results are the percentage of time at pH <4; values in parentheses are ranges

There was no significant difference between ranitidine alone or in combination with metoclopramide Surgery was superior to medical treatment (P<0·05) for the control of upright reflux and for all reflux episodes, and more frequently produced pH results in the normal range. Significant improvements in symptoms occurred after surgery (P<0·05, χ^2), giving more complete control of acid reflux than did medical treatment in refractory gastro-oesophageal reflux.

The effect of introducing endoscopic therapy on surgery and mortality rates for peptic ulcer haemorrhage: a single centre experience of 1102 cases

G.M. Fullarton, G.G. Birnie and W R. Murray, *University Department of Surgery, Western Infirmary, and Department of Medicine, Gartnavel General Hospital, Glasgow, UK*

The introduction of early endoscopic diagnosis has not been associated with a reduction in either surgical intervention or overall mortality for peptic ulcer haemorrhage. Recent studies have suggested that endoscopic therapy (endostasis) can reduce rebleeding rates from peptic ulceration. We report a 2-year experience of the influence of endoscopic heater probe (Olympus CD 10Z) therapy on the outcome of patients admitted with peptic ulcer haemorrhage Eight hundred and sixty-two patients admitted with peptic ulcer haemorrhage over a 5-year period (1978/9–1983/5) before endoscopic therapy and 240 patients admitted with peptic ulcer haemorrhage after the introduction of endoscopic therapy (1986–8) were assessed. All the 1102 patients were managed by a joint physician/surgeon team Results for patients with duodenal ulceration and gastric ulceration are shown in the table

	Duodenal ulcers		Gastric ulcers	
	Surgery	Mortality	Surgery	Mortality
Before endostasis (n=862)	55/614 (9%)	18/614 (2·9%)	40/248 (16%)	22/248 (8·9%)
After endostasis (n=240)	9/132 (6·8%)	1/132 (0·8%)	8/108* (7·4%)	3/108* (2·8%)

* P<0·05

The introduction of an endostasis technique to the management of patients with peptic ulcer haemorrhage has been associated with a significant reduction in the surgical intervention rate and overall mortality for gastric ulceration. A similar but non-significant trend has been observed for duodenal ulcer haemorrhage.

Acid, motility and ulcers: a nature study

D.D. Kerrigan, L.A. Houghton, N.W. Read and A.G. Johnson, *University Department of Surgery, Royal Hallamshire Hospital, Sheffield, UK*

Disordered gastroduodenal motility may be implicated in the pathogenesis of duodenal ulceration by promoting prolonged acid contact with the duodenum. Using a multilumen perfused catheter, we recorded pressure activity in the antrum (two sites), pylorus (Dent sleeve) and duodenum (five sites) in 31 subjects: ten with active ulceration, eight healed and 13 healthy volunteers. Intraluminal pH was measured simultaneously in the antrum and duodenum (two sites), correct pH probe/catheter position was continuously verified by measuring transmucosal potential difference at either end of the Dent sleeve. Fasting pH and motor activity recordings for a mean of 75 min (standard error ±3 min), were continued for 224 ± 18 min after ingestion of a 128 g radiolabelled beefburger.

During fasting, the percentage of time that pH fell to <4 in the duodenal bulb was greater in healed than in active ulcers (12·6 per cent (0–46 per cent) *versus* 0·7 per cent (0–22 per cent), median (range), $P = 0·03$). Bulb pH was <4 for 16 per cent (1–54 per cent) of the postprandial period in healed ulcers, compared with 3 per cent (0–20 per cent) in controls and 1·7 per cent (0–8 per cent) in active ulcers (healed *versus* active $P = 0·04$). Emptying of the antrum after ingestion of the beefburger was significantly delayed in healed duodenal ulcer subjects (healed $T_{50} = 197$ min, control $T_{50} = 137$ min, $P = 0·02$) and associated with a trend to antral hypomotility. Active ulcer subjects and controls emptied at similar rates, indicating that impaired gastric motility in healed duodenal ulceration is secondary to increased duodenal acidification. Differences in bulb pH in active and healed ulcers may also explain the typical cycle of spontaneous healing, yet frequent relapse.

Ischaemic injury and acid back-diffusion may be synergic in acute gastric stress ulceration

R. Stuart, T.F. Gorey, E. Kay, P.J. Byrne and T.P.J. Hennessy, *Trinity College Dublin Department of Surgery, St James's Hospital, Dublin, Ireland*

Mucosal ischaemia with accumulation of oxygen free radicals may be a cause of stress ulceration. We have investigated the efficacy of allopurinol (xanthine oxidase inhibitor) and cimetidine in the prophylaxis of stress ulceration. Pylorus-ligation and gastric-fistula models used previously for acid secretion studies are unphysiological.

Wistar rats of mean weight $193 \pm 4·2$ g were stressed by restraint at 4°C for 2 h and gastric pH was monitored continuously with a modified antimony pH probe and corroborated by serial serum gastrin levels. Rats were divided into four groups of 12, which were given: (a) 1 ml normal saline per os (controls), (b) cimetidine 50 mg/kg intramuscularly, (c) allopurinol 15 mg/kg per os, and (d) allopurinol 5 mg/kg intravenously. After killing, gastric lesions were assessed histologically, measured with a microscope eyepiece graticule, and an ulcer index calculated from the product of ulcer numbers and grade.

			Allopurinol	
	Control	Cimetidine	Oral	Intra-venous
Ulcer index	$59·4 \pm 7·7$*	$10·1 \pm 2·01$	$13·5 \pm 2·48$	$5·8 \pm 1·8$
Gastric pH				
Before drug		$2·4 \pm 0·4$	$2·48 \pm 0·27$	$2·86 \pm 0·26$
Before stress	$2·95 \pm 0·26$	$5·6 \pm 0·48$*	$3·03 \pm 0·31$	$3·08 \pm 0·21$
After stress	$2·6 \pm 0·43$	$5·33 \pm 0·5$*	$1·8 \pm 0·22$	$2·67 \pm 0·48$

All values are means ± s.e.m., * $P < 0·01$, Student's *t* test

Serum gastrin (pmol/l) remained unaltered by stress in the control (before $35·6 \pm 3·54$, after $46·3 \pm 7·42$) and allopurinol (before $33·5 \pm 3·68$; after $44·3 \pm 7·28$) groups, but was significantly elevated in cimetidine-treated rats (before $26·67 \pm 2·13$, after $88·1 \pm 12·85$, $P < 0·01$).

Allopurinol prevents stress ulceration without manipulation of gastric pH. It is suggested that this may be achieved by inhibition of xanthine oxidase-dependent free radical production during mucosal ischaemia which, after the compromise of barrier integrity, may allow acid back-diffusion.

An evaluation of modified sham feeding as a test for completeness of vagotomy

I.G. Martin, M.J. Rogers and D. Johnston, *University Department of Surgery, The General Infirmary, Leeds, UK*

The insulin test has been well documented as a test for completeness of vagotomy. However, the stimulus to acid secretion produced by insulin is not purely vagal in nature and insulin hypoglycaemia is not without hazard. The use of a modified sham feed chew and spit technique has been evaluated in 37 patients undergoing highly selective vagotomy for duodenal ulcer.

Before operation, all 37 patients had BAO, PAO^{Pg}, and PAO^{SF} measured. From 7 to 9 days after operation BAO, and PAO^{SF} and, on another day, BAO and PAO^{I} were measured. Before operation (vagi intact), a median increase in hydrogen ion concentration of 29 mmol/l (upper quartile (UQ) 35 mmol/l, lower quartile (LQ) 20 mmol/l) occurred within 45 min of starting sham feeding. Median PAO^{SF} was 18 mmol/h (UQ 27, LQ 12). After vagotomy, PAO^{I} correlated well with PAO^{SF} (Rank Spearman = 0·53, $P < 0·001$). Using Hollander's criteria, eight insulin tests were positive (1 early, 7 late). Using a rise of 15 mmol/l to indicate incomplete vagotomy, 10 of the sham feeding results were positive (6 positive, 4 negative insulin tests). The median acid response to sham feeding (minus BAO) after vagotomy was 0 mmol/h (UQ 0·16, LQ 0), nine patients had an increase of >0·5 mmol/h and five an increase of >1 mmol/h, all nine were also positive on the concentration response to sham feeding. Two patients have developed recurrent ulcer: both were insulin positive and both on sham feeding had an increase in acid concentration of >15 mmol/l and both had an acid response of >0·5 mmol/h.

In conclusion, sham feeding correlates with the insulin test and incomplete vagotomy is indicated by a rise in concentration >15 mmol/l or an increase in acid output of greater than 0·5 mmol/h, providing a safe and well tolerated alternative to the insulin test.

Oesophageal dysmotility in symptomatic reflux patients with normal endoscopy and pH profile

C.A. Eriksen, P.T. Cullen, D. Sutton, N. Kennedy and A. Cuschieri, *Departments of Surgery and Nuclear Medicine, Ninewells Hospital and Medical School, Dundee, UK*

There is a well known cohort of patients who, despite classical reflux symptoms, have a normal oesophageal pH profile and endoscopy. The management of these patients has proved problematic. In an attempt at determining the pathophysiology of this subgroup, we investigated the oesophageal transit, using a radiolabelled solid egg bolus technique[1] in 58 such patients: 25 men, 33 women, mean age 39·5 years (range 13–65).

The egg transit was normal in 30 patients (52 per cent). In the remaining 28 patients (48 per cent), the condensed image analysis showed the following specific abnormal transit patterns[2]: 'step' delay pattern, demonstrating segmental hold-up in mid- or distal oesophagus in 16 (57 per cent), non-specific delay in six (21 per cent), oscillatory pattern in three (11 per cent), and total non-clearance during the study period (4 min) in three (11 per cent). No significant correlation was found between transit pattern and symptom score (heartburn, Tau −0·115; regurgitation, Tau −0·013, dysphagia, Tau 0·097, Kendall correlation coefficient).

This study shows that almost 50 per cent of patients with reflux symptoms and negative pH and endoscopy have abnormal oesophageal transit, and almost two-thirds of these abnormal patients display segmental transit delay in the lower half of the oesophagus. The effect on symptomatology by prokinetic agents in this patient sub-group needs evaluation.

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2. Eriksen CA, Holdsworth RJ, Sutton D *et al.* The solid bolus oesophageal egg transit test: its manometric interpretation and usefulness as a screening test. *Br J Surg* 1987; **74**: 1130–3

Is the oesophageal body more important than the lower oesophageal sphincter in the pathogenesis of reflux oesophagitis?

L.R. Jenkinson, T.L. Norris and A. Watson, *Department of Surgery, Royal Lancaster Infirmary, Lancaster, UK*

DeMeester[1] has shown that manometric techniques can be used to detect an incompetent lower oesophageal sphincter (pressure ≤6 mmHg, intra-abdominal length <1 cm or sphincter length <2 cm). Similarly, recent combined fluoroscopic and manometric studies have shown that oesophageal clearance is prolonged when peristaltic amplitude is <30 mmHg in the distal oesophagus[2] We have investigated the manometric function of the lower oesophageal sphincter and distal oesophagus using these definitions of incompetence to assess the role of each in the pathogenesis of gastro-oesophageal reflux and their relationship to a hiatus hernia.

A consecutive series of 64 patients with gastro-oesophageal reflux or its complications were evaluated using perfusion manometry. Thirty-seven patients (58 per cent) had peristaltic failure, 29 (45 per cent) had an incompetent cardia and 47 (73 per cent) had a hiatus hernia; 38 (59 per cent) had a combined oesophageal abnormality and a hernia, all three being present in 18 (28 per cent). Isolated incompetence of the cardia in two patients (3 per cent) or peristaltic failure in six (9 per cent) were uncommon. A hernia was the only abnormalty in nine patients (14 per cent) Overall 56 patients (88 per cent) had a manometric defect or a hernia.

This study has shown that peristaltic failure is the most common oesophageal abnormality in patients with gastro-oesophageal reflux. This suggests, contrary to current belief, that the distal oesophagus may be the main protective mechanism and not the lower oesophageal sphincter

1 Zaninotto G, DeMeester TR, Schwizer W, Johansson K-E, Cheng S-C The lower oesophageal sphincter in health and disease *Am J Surg* 1988; **155**. 104–11

2 Kahrilas PJ, Dodds WJ, Hogan WJ Effect of peristaltic dysfunction on esophageal volume clearance. *Gastroenterology* 1988, **94**: 73–80

Monoclonal antibody staining of benign breast tissue components acts as a marker for breast carcinoma

S.P. Courtney, S. Williams and R.E. Mansel, *Departments of Surgery and Pathology, University of Wales College of Medicine, Cardiff, UK*

Monoclonal antibodies 323A3 and Ca1 have been suggested as markers of cancer risk in benign breast disease. The staining characteristics of these antibodies have been studied in ducto-lobular and apocrine tissue in 79 patients with breast carcinoma and in 77 patients with benign breast biopsies.

All the sections studied contained ducto-lobular tissue. Apocrine metaplasia was located in 35 of the malignant biopsies and 42 of the benign biopsies

323A3 antibodies stained strongly the cytoplasm of apocrine metaplasia associated with breast cancer biopsies in 18 of 35 cases, whereas in the benign biopsies only 2 of 42 stained strongly. This difference was statistically significant ($P<0{\cdot}001$, χ^2). By contrast, apical membrane-staining of apocrine tissue by Ca1 antibodies was strong in all 42 benign biopsies, but only 23 of 35 stained strongly in the malignant group ($P<0{\cdot}001$, χ^2).

Malignant breast disease is associated with enhanced expression of the 323A3 antibodies but inhibits expression of Ca1 antigen in apocrine metaplasia. If these changes pre-date the development of overt malignancy they may be useful as markers of breast cancer risk.

Does choice of treatment affect psychological morbidity in early breast cancer? A three-year prospective study

L.J. Fallowfield, A Hall, M. Baum and P.G. Maguire, *CRC Clinical Trials Centre, King's College Hospital, London, UK*

Psychiatric morbidity following mastectomy has been well documented Assumptions that the primary cause is breast loss have not been supported by psychological studies comparing mastectomy with breast-conserving procedures[1] Women who have lumpectomy followed by radiotherapy also experience affective disorders due to fear of cancer and possible recurrence There is evidence that giving women choice concerning treatment options reduces psychiatric morbidity[2,3], although studies to date are small, with short-term follow-up We report preliminary data from a prospective study of 268 women with early breast cancer treated at 10 centres The participating surgeons are grouped according to whether they offer as primary therapy mastectomy, lumpectomy, or a choice of treatment wherever possible

Rates of anxiety and depression were high postoperatively and 3 months later amongst patients of surgeons preferring mastectomy and lumpectomy, irrespective of the actual treatment performed. These rates were considerably lower amongst the patients of 'choice' surgeons where morbidity was largely attributable to those patients unable to exercise choice for 'technical' reasons

These results must be viewed cautiously. giving patients more responsibility for treatment decisions means that they may also feel responsible for outcome, especially if disease progresses. The effect that choice of treatment has on psychological morbidity can only be assessed with long-term follow-up

1 Fallowfield LJ, Baum M, Maguire GP Effects of breast conservation on psychological morbidity associated with diagnosis and treatment of early breast cancer. *Br Med J* 1986, **293**· 1331–4.

2. Ashcroft JJ, Leinster SJ, Slade PD. Breast cancer. patient choice of treatment· preliminary communication *J R Soc Med* 1985; **78** 43–6.

3 Morris J, Royle GT. Choice of surgery for early breast cancer pre- and post-operative levels of clinical anxiety and depression in patients and their husbands. *Br J Surg* 1987, **74**· 1017–19

A randomized controlled trial of medroxyprogesterone acetate in mastalgia

P.R. Maddox, B.J. Harrison, R.E. Mansel, J.M. Horrobin* and P.E. Preece*, *University Departments of Surgery, Cardiff and *Dundee, UK*

There is currently much controversy on the role of luteal deficiency and progesterone replacement in the treatment of mastalgia[1], but no controlled trial has been reported We have carried out a double-blind controlled cross-over study giving 20 mg of medroxyprogesterone acetate (MPA) daily to 26 patients over a period of 6 months. Symptomatic response was assessed objectively by clinical examination and subjectively by a linear analogue scale

Eight patients withdrew from the study during the 6 months of treatment. four were on placebo, one had intolerable side-effects, one became pregnant, and two were non-compliant. The remaining 18 patients showed no significant relief of pain or tenderness on placebo or active treatment, irrespective of the order of treatment

	Clinical score	Linear analogue scale	
	Tenderness mean ± s.d.	Tenderness mean ± s d. (mm)	Pain mean ± s d (mm)
MPA-first group (*n* = 9)			
Pre-trial	2·0 ± 0·5	79·7 ± 26·4	74·7 ± 28·2
End of MPA period	1·7 ± 0·7	61·9 ± 33·6	58·1 ± 34·7
End of placebo period	1·9 ± 0·8	56·9 ± 38·8	43·3 ± 33·2
Placebo-first group (*n* = 9)			
Pre-trial	2·0 ± 0·7	88·3 ± 8·3	78·4 ± 13·6
End of placebo period	1·9 ± 0·8	71·4 ± 28·2	55·9 ± 30·9
End of MPA period	2·1 ± 0·9	63·0 ± 35·4	56·4 ± 37·9

There was no significant difference in MPA scores when compared with pre-trial or after placebo. Also no evidence of progesterone deficiency or prolactin abnormality was found on evaluation of serum taken before and both on and off therapy. Side-effects occurred in 11 patients (five on placebo, five on active treatment and one whilst on both) and were mostly vague premenstrual symptoms

We conclude that the therapeutic response of MPA in cyclical mastalgia is no better than placebo, and that progestogen supplementation can no longer be recommended for routine use in the management of breast pain

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The pro-enzyme form of urokinase: an important factor in human malignant breast disease?

D.A.P. Cooke, M. Mahmoud-Alexandroni*, P.J. Gaffney* and K.G. Burnand, *Department of Surgery, United Medical and Dental Schools, St Thomas' Hospital, London and *National Institute of Biological Standards and Control, Potters Bar, Hertfordshire, UK*

Tissue urokinase (uPA) activity is linked with malignancy. Cells produce uPA as a single-chain pro-enzyme (sc-uPA) which does not bind with plasminogen activator inhibitor (PAI) A high-affinity cell-surface receptor has been identified which binds sc-uPA It has been suggested that bound sc-uPA is converted to two-chain urokinase (tc-uPA) which is protected from PAI, unlike the rapidly inactivated free tc-uPA, and that on the cell surface the tc-uPA can modulate cellular processes or produce fibrinolysis in the micro-environment.

We examined sc-uPA activity in 45 breast biopsies (23 malignant, 22 benign). Cryofragmented samples were extracted into buffered saline and the plasminogen activators were estimated by bioimmunoassay. The sc-uPA was captured by a highly specific monoclonal antibody and detected by a chromogenic substrate solution. A similar system was used to measure tc-uPA activity.

Results shown in the table are in units/mg protein. There was a highly significant difference between the benign and the malignant biopsies in tc-uPA ($t=3{\cdot}582$, d.f. $=43$, $P<0{\cdot}01$) but it was even greater for sc-uPA ($t=5{\cdot}940$, *d.f.* $=43$, $P<0{\cdot}0001$).

	Benign	Malignant
sc-uPA		
Mean	0·155	0·766
Median; range	0·100, <0·1–1·301	0·659, <0·1–2·597
tc-uPA		
Mean	0·398	1·709
Median; range	0·139; <0·015–1·559	1·501, 0·023–6·630

These data support the hypothesis that sc-uPA may be more relevant in malignant breast disease than tc-uPA. Further studies on sc-uPA and its receptors are necessary to show whether the pro-enzyme is a prognostic determinant.

Humorally mediated bone resorption in breast cancer

M.R. Zeiderman, K. Rogers, M. Beneton and J.A. Kanis, *University Departments of Surgery and Human Metabolism, Northern General Hospital and Royal Hallamshire Hospital, Sheffield, UK*

There is a poor correlation between the extent of metastatic disease and the occurrence and severity of hypercalcaemia of malignancy. Recent reports of increased renal tubular reabsorption of calcium[1] and the identification of a PTH-like peptide from patients with non-metastatic cancer[2] suggest that hypercalcaemia and bone disease may be partly humoral in origin. For this reason we have looked for histological evidence of PTH-like activity in the bone of women with non-metastatic breast cancer at the time of their first presentation.

Eight women (mean age 45 years) were studied. None had clinical, radiological or scintigraphic evidence of skeletal metastases. Transiliac bone biopsies were obtained by trephine at the time of definitive breast surgery. Quantitative bone histology[1] was compared with measurements from eight women without breast disease who had recently been admitted for cholecystectomy.

Resorption surfaces of bone were significantly greater in the patients with breast cancer than in controls (rough crenated surface $17{\cdot}0\pm1{\cdot}9$ *versus* $9{\cdot}5\pm0{\cdot}9$ mm per cent total trabecular surface (TTS), $P<0{\cdot}003$ Mann–Whitney U, reversal surface $14{\cdot}6\pm1{\cdot}7$ *versus* $8{\cdot}1\pm0{\cdot}7$ mm per cent TTS, $P<0{\cdot}003$). In addition, the rate of bone formation, as judged by *in vivo* tetracycline labelling, was lower in breast cancer patients ($0{\cdot}028\pm0{\cdot}002$ *versus* $0{\cdot}038\pm0{\cdot}007$ per cent TTS).

These data provide further evidence for the existence of humoral factors in breast cancer capable of influencing bone metabolism even at an early stage of disease.

1. Percival RC, Yates AJP, Gray RES *et al*. Mechanisms of malignant hypercalcaemia in carcinoma of the breast. *Br Med J* 1985; **291**: 776–9.
2. Burtis WJ, Wu T, Bunch C *et al*. Identification of a novel 17000-dalton parathyroid hormone-like adenylate cyclase-stimulating protein from a tumour associated with humoral hypercalcaemia of malignancy. *J Biol Chem* 1987; **262**: 7151–6.

The role of tamoxifen in the primary management of elderly women with breast cancer

T. Bates, D.L. Riley, J. Houghton and M. Baum (on behalf of the Elderly Breast Cancer Working Party), *CRC Clinical Trials Centre, King's College School of Medicine and Dentistry, London, UK*

Patients over the age of 70 have been randomly selected for treatment by either tamoxifen alone (40 mg daily, $n=170$) or 'optimal' surgery plus tamoxifen ($n=163$), with a median follow-up of 34 months.

As progression in the conservatively treated group cannot be compared with local recurrence in the surgical group, 'changes of management' (COM) have been recorded. Forty-four (26 per cent) COM have been observed in the group receiving tamoxifen alone, 36 being due to local or regional progression, 27 (61·4 per cent) underwent subsequent surgery. In the surgical group 29 patients (18 per cent) had COM, 17 being due to local or regional recurrence, 19 (66 per cent) underwent further surgery.

Of the conservatively treated group, 126 are assessable for measurement of tumour response, 19 of these (15 per cent) obtained a complete remission by 6 months, and in 28 (22 per cent) 'best ever response' was observed. The latter was recorded for 16 patients who gained a partial remission (13 per cent), 68 (54 per cent) with static disease and 14 (11 per cent) with progression (tumour >25 per cent initial size). Almost 90 per cent of the conservatively treated group have been maintained for at least 6 months by tamoxifen therapy alone, although more have subsequently undergone a change of management. There is no difference in survival.

In contrast to the two contradictory reports on the primary management of breast cancer in the elderly already published[1,2], we feel it is premature to make firm therapeutic recommendations.

1. Gazet JC, Markopoulos CH, Ford HT, Coombes RC, Bland JM, Dixon RC. Prospective randomised trial of tamoxifen *versus* surgery in elderly patients with breast cancer. *Lancet* 1988; i: 679–81.
2. Robertson JFR, Todd JH, Ellis IO, Elston CW, Blamey RW. Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer. *Br Med J* 1988; **297**: 511–14.

An evaluation of triple-node biopsy in staging breast cancer

R.S. du Toit, A.P. Locker, C.W. Elston, I.O. Ellis and R.W. Blamey, *Nottingham City Hospital, Nottingham, UK*

Six hundred and ninety-three patients with early breast cancer treated by primary surgery and a triple-node biopsy technique of the draining lymph nodes have been reviewed to determine the prognostic value of adding the apical and/or internal mammary node to sampling of the lower axillary nodes. One node each was sampled from the lower axilla, the apex of the axilla and the second intercostal space.

Results showed that the positive node rate of each node location increased with an increase in tumour size. Lateral tumours (70 per cent) gave significantly more positive lower axillary and apical nodes than medial tumours. Medial tumours (15 per cent) gave significantly more positive internal mammary nodes than lateral tumours. No differences in node positive rates between apical and internal mammary nodes could be found for centrally located tumours.

Cases with a positive apical node had been shown previously to have a poor prognosis. Involvement of the internal mammary node alone was associated with the same prognostic value as involvement of the lower axillary node alone. When both of these two nodes were positive the prognosis deteriorated to that of a positive apical node.

Additional prognostic information was gained in 12·8 per cent of cases with laterally located tumours if the apical node was sampled in addition to that of the lower axilla; and in 17·6 per cent of cases with medially located tumours if the internal mammary node was sampled in addition to the lower axillary node.

The prognostic information gained justifies the policy of triple-node biopsy.

Relationship of in vitro response to gastrin, gastrin receptor status and ability to secrete gastrin in gastrointestinal cancer cells

S.A. Watson, L.G. Durrant and D.L. Morris*, *Department of Cancer Research, Nottingham University, and *Department of Surgery, University Hospital, Nottingham, UK*

A series of gastrointestinal tumour cell lines were screened for their *in vitro* growth response to human gastrin (G–17) by ^{75}[Se]selenomethionine incorporation.

In vitro growth response was shown in a rat pancreatic (AR42J) and a human gastric (MKN45) cell line which responded to G–17 by enhanced label incorporation (195 and 145 per cent of control). Of three human colorectal cell lines examined, HT29 responded moderately (123 per cent) whereas C280 and C146 did not respond to the hormone.

Gastrin receptors were measured in the above cell lines using ^{125}[I]G–17. AR42J had $1{\cdot}5\times10^5$ specific gastrin-binding sites per cell, MKN45 had 3×10^3, and the colorectal lines had no measurable sites.

Gastrin production by the cell lines during *in vitro* growth was analysed by a radioimmunoassay using an antigastrin antiserum. An inverse relationship between gastrin response and gastrin production *in* *vitro* was observed. No gastrin was detected in the cell culture medium after growth of AR42J (the most gastrin-responsive cell line) whereas 44 to 37 ng litre^{-1} cells^{-5} per day of gastrin was measured in the medium after growth of C146 and C280 (non-gastrin responsive cell lines). MKN45 responded to and produced modest levels of gastrin (11·5 ng litre^{-1} cells^{-5} day^{-1}). Gastrin receptor status appears to be correlated with the ability of cancer cells to respond to gastrin but perhaps inversely to their ability to secrete gastrin.

Glucocorticoids mediate the catabolic effects of tumour necrosis factor during critical illness

K. Mealy, J.J.B. Van Lanschot and D.W. Wilmore (introduced by T.P.J. Hennessey), *Department of Surgery, Brigham, and Women's Hospital and Harvard University, Boston, USA*

Cytokines and hormonal mediators contribute to the metabolic response of critical illness. To investigate the interaction between these agents, we administered tumour necrosis factor (TNF: 0, 2 and 4×10^5 units kg^{-1} 24 h^{-1}) to 40 male Wistar rats to determine the adrenal response. Adrenal weight increased with dose of TNF ($P<0·001$). We then administered TNF (2×10^5 units kg^{-1} 24 h^{-1} intravenously) or corticosterone (CC, 75 mg pellets subcutaneously) to rats maintained on a constant intravenous diet over 7 days. Daily nitrogen balance was determined and organ and carcass composition measured at the time of killing. A portion of the data is shown (mean ± s.e.m.)

	Control ($n=9$)	CC ($n=7$)	TNF ($n=11$)
Carcass nitrogen (g)	2·58 ± 0·09	2·06 ± 0·18	2·19 ± 0·10*
Liver nitrogen (mg)	268·4 ± 19·0	283·0 ± 7·9	440·0 ± 30·0*†
Ureagenesis (mg 6 days^{-1})	1428 ± 92	2280 ± 209*	2182 ± 115*
Nitrogen balance (mg 6 days^{-1})	987 ± 91	125 ± 209*	224 ± 123*
Jejunal mucosal DNA (µg cm^{-1})	141·2 ± 11·8	124·4 ± 11·7	87·3 ± 7·0*†
Jejunal mucosal protein (mg/cm)	1·86 ± 0·17	1·80 ± 0·19	1·3 ± 13*†

* $P<0·01$ *versus* control († $P<0·01$ *versus* CC) by ANOVA (Dunnett *t* test).

Plasma corticosterone in CC and TNF groups were similar when the rats were killed (24·8 ± 2·7 *versus* 16·1 ± 2·2 µg dl^{-1}). Both CC and TNF increased peripheral proteolysis as determined by decreased carcass nitrogen content and diminished nitrogen balance. TNF alone increased liver mass and caused substantial destruction of the intestinal tract. TNF mediates many of the major metabolic sequelae of critical illness. However, its effects on skeletal muscle can be explained by activation of the hypothalamic/adrenal stress response.

Taurolidine improves survival in rats with established peritonitis

P.D. Carey, T.M. Feeley, P. Marks, F.B. Keane and W.A. Tanner, *Department of Surgery, Meath Hospital, and Trinity College, Dublin, Ireland*

Sepsis remains the cause of considerable mortality despite the use of powerful antibiotics. Many potent antiseptic agents have been developed but hitherto none was suitable for systemic administration. Taurolidine is a new antiseptic suitable for intravenous administration. Having previously reported the potent anti-endotoxin effects of taurolidine in the jaundiced rat we have, in this study, assessed the effects of taurolidine in a septic rat model.

Sixty male rats were subjected to laparotomy, and peritonitis was induced by double puncture of the ligated caecum using an 18 gauge needle. Animals were randomly divided into treatment and control groups and were given either taurolidine 100 mg/kg or an equal volume of saline, intravenously, at 6 h and 12 h after laparotomy.

In the control group 16 (53 per cent) animals were dead 24 h after laparotomy compared with two (7 per cent) in the treatment group ($P<0·0001$). At 48 h, 26 control and 17 treatment animals were dead ($P<0·01$). No animals died during the following 24 h in either group. Overall survival in the taurolidine group was significantly greater than in controls ($P<0·01$).

We conclude that taurolidine is an effective antiseptic in the treatment of established peritonitis in this animal model.

Bipolar electrocoagulation: short or long blasts?

J.D. Harrison and D.L. Morris, *Department of Surgery, Queen's Medical Centre, Nottingham, UK*

The current view regarding bipolar diathermy electrocoagulation is that after short periods of time (around 2 s) the electrical properties of the tissue change, rendering further coagulation ineffective. To test this theory we used the fresh iliac arteries and aortas of lagomorphs, which were excised *in vivo*. The diameter of the vessels was measured with a micrometer, and the experiments were carried out in two groups: those vessels 2–3 mm in diameter, and those 4–5 mm. The vessels were subjected to either 2 or 20 s of electrocoagulation with a BICAP probe and generator at a fixed power setting, using a fixed weight of 500 g applied to the probe head. The bursting pressure of the coagulated vessel wall was determined by cannulating the vessel and gradually increasing the distending pressure (measured with an electronic transducer) until the coagulum seal fractured.

Vessel size (mm)	Time (s)	Pressure (cm) median (range)	Mann–Whitney *U* test	*P*
2–3	2	460 (100–1120)		
($n=22$)	20	760 (360–1140)	158·5	0·038
4–5	2	400 (100–640)		
($n=14$)	20	800 (400–1120)	72	0·015

These data oppose the widely held view that prolonged bipolar diathermy is unproductive, and suggest that more effective haemostasis of bleeding vessels may be achieved by more prolonged use of the diathermy probe.

Is perioperative analgesia important in the genesis of postoperative fatigue?

M.R. Zeiderman, E. Welchew and R.G. Clark, *University Department of Surgery and Department of Anaesthetics, Northern General Hospital, Sheffield, UK*

Persistent tiredness after surgery is common and appears to be related to the magnitude of the operative procedure[1]. Epidural analgesia influences postoperative cardiorespiratory function and reduces the catabolic response to abdominal surgery[2]. This study has examined whether epidural analgesia has a therapeutic role in limiting the development of postoperative fatigue.

Twelve patients admitted for elective abdominal surgery were randomized to receive postoperative analgesia with intermittent intramuscular morphine ($n=6$; four women, two men, age range 27–71 years, median 53 years) or a continuous infusion of epidural fentanyl ($n=6$; three women, three men, age range 27–68 years, median 52 years). Fatigue was assessed on an analogue scale of 1 (fit) to 10 (fatigued). Steady-state measurements of respiratory gas exchange, respiratory rate (f_R) and tidal volume (V_T) were made before operation and repeated on the third postoperative day. Resting energy expenditure (REE) was calculated from Weir's formula.

	Fatigue (units)		REE (kJ day^{-1})		f_R (breaths min^{-1})		V_T (litres)	
	E	NE	E	NE	E	NE	E	NE
Preop	2·5 ± 0·4	2·5 ± 0·4	7223 ± 1162	6679 ± 844	11 ± 1	16 ± 2	0·58 ± 0·09	0·42 ± 0·03
P	<0·001	<0·001	n.s.	n.s.	<0·02	n.s.	n.s.	n.s.
Postop	8·8 ± 0·7	5·8 ± 0·7	6922 ± 1404	6738 ± 301	18 ± 2	18 ± 2	0·44 ± 0·07	0·46 ± 0·04

All results are given as mean ± s.e.m.: Mann–Whitney *U*
E, epidural; NE, non-epidural

Epidural analgesia does not confer any added advantage over intramuscular opiates in limiting the development of postoperative fatigue.

1. Christensen T, Kehlet H. Postoperative fatigue and changes in nutritional status. *Br J Surg* 1984, **71**: 473–6.
2. Brandt MR, Fernandes A, Mordhorst R *et al.* Epidural analgesia improves postoperative nitrogen balance. *Br Med J* 1978; **1**: 1106–8.

Can the energy requirements of burned patients be accurately predicted?

J.K.G. Laitung and J.A.D Settle (introduced by M J. McMahon), *Yorkshire Regional Burns Centre, Pinderfields Hospital, Wakefield, UK*

Calculation of energy requirement from formulae based on body weight and size of burn[1,2] is known to overestimate measured energy expenditure in burned patients[3] The aim of this study was to measure energy expenditure in burned patients and derive an equation to give actual energy requirement from clinical data.

Resting energy expenditure (REE) was measured by indirect calorimetry in 20 patients aged 20–81 (mean 37) years. Their total burn size was 20–65 per cent (mean 35 per cent) and the size of full-thickness burns (per cent FT) 0–60 per cent (mean 15 per cent). Stepwise regression analysis of these and other clinical variables was performed to calculate the best fit prediction of percentage increase in REE above that of the value obtained by the Harris–Benedict formula for normal individuals This yielded the equation

$$32+(0{\cdot}3\times\%\text{FT burn})-(0{\cdot}4\times\text{days after burn})+34\ (\text{if septic})$$

Validation of this formula was carried out in a further 15 patients aged 4–81 years (mean 27 years) with total burn size 8–48 per cent (mean 26 per cent) and full-thickness burn size 0–38 per cent (mean 8 per cent). This showed good correlation between calculated energy expenditure and measured energy expenditure ($r=0{\cdot}83$, $P<0{\cdot}0001$)

	REE (calculated)	REE (measured)
Mean ± s e m	1852 ± 58	1815 ± 61 (kcal/day)

In burned patients, REE can therefore be calculated from clinical data which enables nutritional requirement to be supplied precisely without the use of a calorimeter.

1 Curreri PW, Richmond D, Marvin J, Baxter CR. Dietary requirements of patients with major burns *J Am Diet Assoc* 1974; **65** 415–8

2 Sutherland AB Nitrogen balance and nutritional requirements in the burn patient a reappraisal *Burns* 1976, **2**· 238–44

3 Turner WW, Ireton CS, Hunt JL, Baxter CR Predicting energy expenditures in burned patients. *J Trauma* 1984, **25** 11–16

Risks of an intracranial haematoma in head-injured adults and children

G. Teasdale, G. Murray, E Anderson and D Mendelow, *Institute of Neurological Sciences, Glasgow, UK*

Knowing the risks of developing an intracranial haematoma for different groups of head-injured patients can lead to earlier detection, improved outcome and more efficient management. We have therefore extended, to children, previous work that identified the importance of a skull fracture in adults[1], and in both groups have also determined the importance of alteration in consciousness Data on these findings were determined in a retrospective series of 1107 patients with traumatic intracranial haematoma admitted from an Accident and Emergency Department (A and E) to a regional neurosurgical unit. Data about the total population at risk were obtained from surveys involving 8406 patients The table shows the occurrence of skull fracture and of altered consciousness in the two groups and the corresponding risk of developing haematoma calculated from the total numbers at risk, using either the method described by Mendelow *et al* [1] or, when multiple factors are considered, by global linear modelling

	Haematomas (%)		A and E sample (%)		Absolute risk	
	Adults	Children	Adults	Children	Adults	Children
No skull fracture						
Fully conscious	4	16	92	95	7900	13 000
Altered consciousness	10	12	5	3	180	580
Coma	8	10	1	3	27	65
Skull fracture						
Fully conscious	10	18	1	1	45	160
Altered consciousness	29	19	1	0·2	5	25
Coma	38	24	1	0·1	4	12

Although children are at less risk than adults, in both groups the presence of a skull fracture is an important indication of the risk of subsequent intracranial haematoma.

1 Mendelow AD, Teasdale G, Jennett B *et al* Risks of intracranial haematoma in head injured adults *Br Med J* 1983; **287**. 1173–6

A new method of quantifying median cerebral cortical transit times

A.R. Naylor, J.M. Slattery, A Notghi, J.D. Miller and M.V. Merrick, *Departments of Clinical Surgery, Clinical Neurosciences and Nuclear Medicine, The Royal Infirmary and Western General Hospitals, Edinburgh, UK*

A new method for quantifying regional median cerebral cortical transit time (MCTT), which corrects for the error due to dispersion of the bolus following intravenous injection of pertechnetate, was validated against middle cerebral artery velocities measured using transcranial Doppler ultrasound Reproducibility (of 3 studies) and the response to hyperventilation and rebreathing were studied in 13 normal volunteers (aged 25–54 years).

Both techniques were reproducible, with the coefficients of variation being 5·7 per cent for MCTT and 6·3 per cent and 6·8 per cent for peak and mean velocity respectively There was a linear relationship between end-tidal CO_2 (ET_{CO_2}), and MCTT ($r=0{\cdot}84$, gradient $=-1{\cdot}47$ per 1 per cent change in ET_{CO_2}), peak velocity ($r=0{\cdot}81$, gradient $=15{\cdot}5$ cm/s per 1 per cent change in ET_{CO_2}) and mean velocity ($r=0{\cdot}86$, gradient $=13{\cdot}6$ cm/s per 1 per cent change in ET_{CO_2}) There was no significant difference in slope gradients between individuals, and the wide range of normal MCTT for a given end-tidal CO_2 was caused by interindividual variation. The mean interhemispheric MCTT difference was $0{\cdot}25\pm0{\cdot}22$ s A previously unconfirmed relationship between velocity and MCTT was demonstrated· under normal physiological conditions, peak velocity was proportional to the inverse of hemispheric MCTT, which in turn represents the ratio of blood flow to blood volume

Hypoxia and hypotension during colonoscopy and endoscopy

J.F. Lancaster, D.C Bartolo and D J. Leaper, *Department of Surgery, University of Bristol, UK*

Cardiac arrhythmias and hypoxia have been described in 30 per cent of endoscopies and account for 60 per cent of deaths We have performed studies to determine whether cardiopulmonary disturbance is also a feature of large bowel fibreoptic examination and whether such changes are predictable

Sixty patients undergoing endoscopy ($n=30$) and colonoscopy ($n=30$) had continuous monitoring of arterial oxygen saturation (S_{a,O_2}), pulse and mean blood pressure (BP) The degree of patient distress, duration, dose of sedative and details of the endoscope and operator were recorded.

Marked hypotensive (>40 per cent fall BP) and hypoxic (>8 per cent fall S_{a,O_2}) changes occurred in 13 per cent and 16 per cent of the group respectively There were no significant differences in fall in BP, S_{a,O_2} or pulse between the endoscopy and colonoscopy groups The dose of sedative was significantly related to the fall in S_{a,O_2} ($P<0{\cdot}001$) but not to the fall in BP Falls in S_{a,O_2} and BP were both related to the duration of the procedure ($P=0{\cdot}01$). There were no correlations between the degree of hypoxia or hypotension and the patient's age or previous medical history

Hypotension and hypoxia occur in both colonoscopy and endoscopy and are neither predictable nor usually recognizable clinically We recommend pulse, oximetric and BP monitoring throughout gastrointestinal endoscopy for maximal patient safety

Breath-hydrogen testing: an indicator of small bowel overgrowth following pouch formation

W.A. Kmiot, J.D. O'Brien and M.R.B Keighley, *The General Hospital, Birmingham, UK*

The absolute number of bacteria per gram of ileal chyme and the anaerobic to aerobic ratio increase after ileal reservoir construction. The production of hydrogen by anaerobic fermentation is a recognized measure of small intestinal bacterial overgrowth

After restorative proctocolectomy 30 patients performed a series of breath-hydrogen estimations at 5-min intervals for 1 h A further 30, matched for age and sex, were tested as controls. All subjects fasted for a minimum of 20 h

Patients with ileal reservoirs had a higher mean fasting breath-hydrogen value than control subjects (16·4 *versus* 5·7 parts per million (p.p.m.), $P < 0{\cdot}05$) Six 'pouch' patients did not exhibit a rise in breath hydrogen either on repeated tests or on instillation of isotonic glucose directly into the pouch These patients had significantly lower faecal bacterial counts (2×10^6) than the remaining 24 patients who exhibited rises in breath hydrogen of at least 20 p.p.m (faecal count 9×10^6, $P < 0{\cdot}02$) All patients with a fasting breath-hydrogen level of >10 p.p.m. had anaerobic bacterial pouch overgrowth ($>10^7$ colony forming units per gram), compared with none of the remainder ($P < 0{\cdot}05$) There was no relationship between pouch overgrowth and the frequency of defaecation This study confirms that fasting non-invasive breath-hydrogen sampling acts as a sensitive indicator of ileal bacterial overgrowth following pouch formation.

Relationship between bile acid malabsorption using ^{75}SeHCAT scanning method and diarrhoea following right hemicolectomy: evidence for intestinal adaptation

A.J. Jewkes, C.W.O. Windsor, R.S. Ward and A.E. Timmins (introduced by J. Neoptolemos), *Departments of Surgery and Nuclear Medicine, Royal Infirmary, Worcester, UK*

Diarrhoea following right hemicolectomy occurs in up to 50 per cent of patients[1] Malabsorption of bile acids due to resection of the terminal ileum is thought to be important in the pathogenesis of these post-operative symptoms, but has been inadequately studied

In a prospective study, the bile acid pool was examined using 7-day ^{75}SeHCAT scanning in 21 patients in order to evaluate the temporal relationship between bile acid malabsorption and diarrhoea following right hemicolectomy[2]. Patients were imaged preoperatively and in the early (2–11 weeks) and late (44–80 weeks) postoperative periods Stool frequency was also recorded at the time of each scan.

The median preoperative ^{75}SeHCAT retention ratio was 44·3 per cent (range 17–73 per cent, normal value >19 per cent) compared with the significantly lower early postoperative values (3·5 per cent; 0–15 per cent) and the late postoperative values (3·0 per cent; 0–14·5 per cent) (both $P < 0{\cdot}001$; two-tailed Mann–Whitney *U* test). In the early postoperative period 10 out of 21 (48 per cent) patients had diarrhoea (median stool frequency 4/day, range 0·5–10/day) compared with only 3 out of 18 (17 per cent) in the late postoperative period (2/day, 0·33–6/day) ($P = 0{\cdot}013$) The correlation between the length of small bowel resected and the degree of diarrhoea was not significant in either the early ($r = 0{\cdot}17$) or late ($r = 0{\cdot}21$) postoperative periods. There was also no significant correlation between the degree of diarrhoea and bile acid malabsorption (early $r = 0{\cdot}13$ and late $r = 0{\cdot}05$).

These original findings suggest that despite continuing bile acid malabsorption, intestinal adaptation occurs, resulting in a significant reduction in stool frequency, the mechanisms require elucidation

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Is intractable constipation associated with a systemic autonomic neuropathy?

D.J Waldron, N.S. Williams, D. Kumar, R.I. Hallan and M. Swash*, *Departments of Surgery and *Neurology, The London Hospital, London, UK*

Patients with intractable constipation often have symptoms suggesting a multisystem disorder Do they have a systemic disturbance of autonomic nerve function? Eight patients with intractable constipation and six controls underwent assessments of autonomic cardiovascular reflexes – fall in systolic blood pressure on standing (SBPS), ratio of heart rate between the 30th and 15th beat after standing (RHRS), variation in heart rate with deep breathing (VHRB) and ratio of the slowest heart rate following to the fastest rate during a Valsalva manoeuvre (RHRV) Results were compared with conventional normal ranges (CNR).

SBPS pressure did not differ between controls and constipated patients ($8{\cdot}3 \pm 2{\cdot}1$ *versus* $9{\cdot}2 \pm 2{\cdot}4$ mmHg, $P > 0{\cdot}5$, CNR being <30 mmHg) VHRB was $27{\cdot}6 \pm 6{\cdot}5$ in controls *versus* $21{\cdot}5 \pm 2{\cdot}8$ in constipated patients ($P > 0{\cdot}4$), none being less than the CNR of >10 While there was a significant difference during RHRV ($1{\cdot}9 \pm 0{\cdot}1$ for controls *versus* $1{\cdot}4 \pm 0{\cdot}1$ in constipated patients, $P < 0{\cdot}02$), this was only in degree of normality as indicated by a CNR ratio >1·1 No significant difference in RHRS was seen ($1{\cdot}03 \pm 0{\cdot}01$ for controls *versus* $0{\cdot}97 \pm 0{\cdot}04$ in constipated patients, $P > 0{\cdot}2$), but four of eight patients as opposed to one of six controls had ratios outside the CNR of 1·0.

Half the constipated group had an abnormality of one test of autonomic nerve function Generalized autonomic neuropathy may thus be an aetiological factor in a subgroup of patients with intractable constipation.

Prognostic value of nucleolar organizer regions and ploidy status in advanced colorectal cancer

K. Moran, T. Cooke, G. Forster, P. Gillen, S Sheehan, P. Dervan and J M. Fitzpatrick, *Departments of Surgery and Pathology, Mater Hospital, Dublin, and Royal Liverpool Hospital, UK*

Conventional clinical and pathological prognostic parameters are inaccurate in colorectal cancer One third of patients with Dukes' B carcinoma die while one third of those with Dukes' C survive long term, irrespective of histological differentiation[1,2]. We studied the prognostic value of nucleolar organizer regions (NORs) and ploidy status and their correlation with established prognostic parameters in advanced colorectal cancer Fifty-one patients aged 35–81 years (mean 61·6 years) with Dukes' C tumours (eight with liver metastases) were studied All were followed for a minimum of 5 years. Sections from primary tumours and lymph node metastases (LN) were stained for NORs Ploidy status was determined for primary tumours in 40 patients using flow cytometry. NOR and ploidy status were correlated with age, sex, histological differentiation, presence of liver metastases and survival time, and the independent significance of prognostic variables was determined using Cox's multivariate regression analysis. NORs and ploidy values did not correlate with age or sex. Sixteen patients who survived 5 years had lower NOR counts than non-survivors ($P < 0{\cdot}05$; Mann–Whitney *U* test) Survivors had a lower percentage of aneuploid tumours. NORs were the most important individual variable for predicting survival ($P < 0{\cdot}05$). Ploidy values correlated with histological differentiation and liver metastases.

	Survivors		Non-survivors	
	Primary	LN	Primary	LN
NOR, median (range)	12 (8–15)	11 (8–15)	17 (14–25)	18 (13–25)
Ploidy (percentage aneuploid)	40		57	

We concluded that NORs were more accurate and ploidy values were as accurate as conventional clinical and pathological parameters in predicting 5-year survival in advanced colorectal cancer

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Growth autonomy and invasiveness in vitro of human colorectal carcinoma cells

N. Williams, J. Daly and M. Herlyn (introduced by D. Bouchier-Hayes), *The Wistar Institute of Anatomy and Biology and the Department of Surgery, University of Pennsylvania, Philadelphia, USA*

Growth autonomy and invasion play important roles in the progression of colorectal carcinoma to the metastatic stage. Growth autonomy *in vitro* is defined as the ability of cells to survive and proliferate in the absence of exogenously added growth factors In this study, five colorectal carcinoma cell lines were adapted over a 4-month period to growth in medium W487 without growth factors and other proteins, and examined for changes in expression of tumour-associated antigens and in invasiveness through a reconstructed basement membrane (Matrigel) Antigen expression on carcinoma cells was determined by a fluorescent analysis cell sorter using a panel of monoclonal antibodies Invasiveness *in vitro* was measured as the ability of cells to invade a reconstructed basement membrane in the Boyden chamber chemoinvasion assay In each of these experiments, the cell line adapted to grow in protein-free medium was compared with the parent cell line which was maintained in W487 medium supplemented with exogenous growth factors and 2 per cent fetal calf serum (FCS) There were no significant differences in tumour-associated antigen expression between the adapted cell lines and the parental cell lines. The results of the invasion assays (mean ±s.d.) are expressed as the number of cells per high power field (HPF) that migrate through the basement membrane.

	Number of cells/HPF				
W487 medium	SW 403	SW 1116	SW 48	SW 948	NWG 1
With FCS	5·7±3·1	1·1±0·8	4·2±3·2	3·0±1·9	5·8±1·7
Protein-free	23·0±3·7*	19·1±3·7*	12·5±5·9*	1·5±1·1	3·6±1·6
Fold increase	4·0	17·4	3·0	—	—

* $P<0{\cdot}001$

The data show that in three of the five cell lines tested there was a significant increase in invasiveness in the cells adapted to protein-free medium when compared with the parental cell line. These results suggest that the acquisition of growth autonomy can increase the invasive capacity of colorectal carcinoma cells *in vitro*.

Monoclonal antibody detection of fibrinolytic activation during salvage autotransfusion

J.F. Thompson, the late P.C. Clifford, J.H.H. Webster and A.D.B. Chant, *Vascular Unit, Royal South Hampshire Hospital, Southampton, UK*

Reinfusion of activated clotting factors during salvage autotransfusion may theoretically lead to coagulopathy. To investigate this possiblity 17 patients have been studied undergoing autotransfusion (non-washed) during elective aortic surgery. Maintenance of adequate intraoperative heparinization was judged by activated clotting time measurements and confirmed by postoperative chromogenic activated factor X assay.

Fibrinolytic activity was measured using immunoagglutination based on a monoclonal antibody directed against fibrin-split products (XDP)[1]. Plasma XDP levels were determined in paired samples from autotransfusion reservoirs, from patients preoperatively, and at 0 h, 4 h and 24 h postoperatively.

Normal XDP (200 ng/ml) was found in all 17 patients preoperatively, while 28 of 32 reservoirs had raised XDP (mean 3770 ng/ml· range 400–24 000). XDP levels were raised in four recipients' plasma immediately postoperatively but did not exceed 500 ng/ml. There was no clinical or other haematological evidence of disseminated intravascular coagulopathy after salvage autotransfusion.

Plasmin activation and subsequent fibrin degradation occurs within reservoirs during autotransfusion, despite high-dose heparinization. However, reinfusion of non-washed blood did not lead to significant activation of fibrinolysis in the patients studied.

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The influence of platelet and leucocyte depletion on pulmonary microembolization during major surgery

D.B. Hocken, D.A.J. Galvin, C.M. Backhouse, R.A Harper and C.N. McCollum, *Department of Surgery, Charing Cross and Westminster Medical School, London, UK*

Platelet and leucocyte microembolization may lead to pulmonary dysfunction after major surgery. A study was therefore carried out to see whether selective preoperative depletion of these cells would reduce pulmonary damage.

Twenty pigs were randomized to selective cell separation (SCS) (Haemonetics V-50 cell separator) or control. Animals underwent standardized aortic surgery consisting of midline laparotomy, and 90-min aortic occlusion. After aortic declamping the animals became hypotensive for 60 min before full resuscitation. Vena caval microaggregate levels were assessed by screen filtration pressure (SFP). Pulmonary vascular resistance (PVR), arterial P_{O_2} (P_{a,O_2}) and alveolar–arterial P_{O_2} difference ($P_{A\text{-}a,O_2}$) were recorded.

	Fall in platelets (×10⁹/l)	Rise in SFP (slope)	Rise in PVR (d-s/cm⁵)	Rise in P_{A-a,O_2} (mmHg)	Fall in P_{a,O_2} (mmHg)
Control	216±43	1·21±0·2	917±76	24·2±2·7	20·8±1·9
SCS	76±25*	0·78±0·2*	380±54*	14·8±3·1*	11·3±1·7*

All results are mean±s.e.m. * $P<0{\cdot}01$, Mann–Whitney *U* test

Cell separation reduced initial mean platelet and leucocyte counts by 75 per cent and 30 per cent respectively ($P<0{\cdot}001$). In control animals there was a significant fall in platelet count during surgery which was reduced by cell separation, whilst at the same time there was a rise in SFP which was inhibited in cell-separated animals. When the cross-clamp was released, PVR rose considerably in controls compared with cell-separated animals. This was associated with an improvement in postoperative pulmonary function in cell-separated animals ($P_{A\text{-}a,O_2}$, P_{a,O_2}).

Selective cell separation prevented recruitment of platelets and leucocytes into microemboli, reduced a rise in PVR and improved postoperative pulmonary function.

Calf pump failure and fibrinolysis

H. Gajraj and N.L. Browse, *Department of Surgery, St Thomas' Hospital Medical School, London, UK*

Venous ulceration is associated with calf pump failure, reduced blood fibrinolytic activity and pericapillary fibrin cuffs (which are thought to block oxygen diffusion) in affected skin[1]. This study investigates the relationship between local tissue fibrinolysis and transcutaneous oxygen tensions (P_{tc,O_2}).

^{125}I-fibrin clots, formed by the injection of 0·05 ml of ^{125}I-labelled fibrinogen and thrombin, were produced in the subcutaneous tissue of the legs of 33 subjects with healed venous ulcers, 10 subjects with bilateral varicose veins and the normal skin of 11 controls. The clearance half-life of the fibrin ($^{125}F_{\frac{1}{2}}$) was calculated for each site. Calf pump function was assessed by foot volumetry, measuring the relative expelled volume (EV_{rel}) and the half-volume refilling time ($TV_{\frac{1}{2}}$). The P_{tc,O_2} of the 'gaiter' skin was measured with a Clarke-type electrode (Radiometer).

	Results (mean and s.d.)	
	$^{125}F_{\frac{1}{2}}$ (h)	P_{tc,O_2} (mmHg)
Controls	18·2 (5·1)	70·6 (7·6)
Subjects with varicose veins	24·7 (6·5)*	75·9 (20·6)†
Subjects with healed ulcers		
Never-ulcerated leg	25·1 (8·9)**	58·3 (17·3)**
Healed leg	36·9 (21·1)***	48·7 (17·4)***

Compared with controls. † not significant, * $P<0{\cdot}05$, ** $P<0{\cdot}01$, *** $P<0{\cdot}001$ (Mann–Whitney *U* test)

Significant negative correlations were found between $^{125}F_{\frac{1}{2}}$ and the P_{tc,O_2} ($P<0{\cdot}01$) and between $^{125}F_{\frac{1}{2}}$ and the $TV_{\frac{1}{2}}$ ($P<0{\cdot}01$). Local interstitial fibrinolysis appears to be related to transcutaneous oxygen tensions and calf pump function.

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The significance of plasma fibrinolytic activity in the development of ulceration in patients with chronic venous insufficiency

S.A. Whawell, T Harbourne, S. Vasdekis, D. Christopoulos, H Clark and A.N. Nicolaides, *Irvine Laboratory for Cardiovascular Investigation and Research, Academic Surgical Unit, St. Mary's Hospital Medical School, London, UK*

It has been suggested that fibrinolytic activity may be an important factor in the development of skin changes and ulceration in limbs with chronic venous hyptertension[1]. Thirty-seven patients with chronic venous problems (varicose veins, liposclerosis and ulceration) have been studied using ambulatory venous pressure (AVP) measurements and euglobulin lysis time[2] corrected to a standard (3 g/l) plasma fibrinogen concentration (ELTc).

Eighteen of the 37 patients had skin changes. four had liposclerosis only and 14 had both liposclerosis and ulceration.

AVP was less than 35 mmHg (normal) in eight patients, none of whom had any skin changes; it was greater than 65 mmHg (severe) in seven patients, six of whom had ulceration, and between 35 and 65 mmHg (moderate) in 22 patients In this moderate group ELTc was less than 240 min in 12 patients of whom two had liposclerosis only, and greater than 240 min in 10 patients of whom nine had liposclerosis and seven had both liposclerosis and ulceration (Fisher's exact test, $P<0·001$)

The results suggest that although venous hypertension is a factor responsible for skin changes, fibrinolytic activity measured by the ELTc is also a major factor which determines whether skin changes will occur in patients with moderate venous hypertension

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Quantitative assessment of venous outflow resistance in the postphlebitic limb

A. Rulo, G. Belcaro and A.N. Nicolaides, *Irvine Laboratory for Cardiovascular Investigation and Research, Adacemic Surgical Unit and Vascular Unit, St. Mary's Hospital Medical School, London, UK*

Venography is the traditional method used to diagnose venous obstruction The purpose of this study was to develop a method for the measurement of venous outflow resistance. Venous occlusion air-plethysmography has been used to measure absolute volume and flow (Q) changes[1] with simultaneous measurement of venous pressure (P) on the release of a thigh cuff inflated to 70 mmHg. Resistance ($R=P/Q$) was calculated at intervals of 0·4 s (in mmHg l^{-1} min^{-1}) during venous emptying. It was compared with a previously described method of evaluation of venous obstruction which measured the arm/foot pressure differential (ΔP) in the supine subject[2].

The results of 10 normal limbs and 18 limbs with venographic obstruction (10 with $\Delta P>5$ mmHg and 8 with a $\Delta P<5$ mmHg) are shown in the table.

	Venous resistance mean ± s d. (mmHg l^{-1} min^{-1})		
		Patients	
Venous pressure	Normal volunteers	$\Delta P<5$ mmHg	$\Delta P>5$ mmHg
15 mmHg	10·3 ± 2·0	18·5 ± 10·4	43·8 ± 10·7
25 mmHg	8·3 ± 1·3	14·0 ± 6·5	31·7 ± 15·9
35 mmHg	8·0 ± 1·3	14·2 ± 6·8	22·2 ± 5·0

Limbs with a $\Delta P>5$ mmHg had a markedly elevated resistance (no overlap with normal volunteers). Patients with $\Delta P<5$ mmHg were in the normal range with the exception of three occupying an intermediate position These results suggest that venous resistance is not constant, but varies with pressure. It should be used as a 'gold standard' to evaluate non-invasive tests and study the natural history of patients with outflow obstruction

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Long-term effect of elastic compression on venous haemodynamics of the leg

D. Christopoulos and A.N. Nicolaides, *Irvine Laboratory for Cardiovascular Investigation and Research, Academic Surgical Unit and Vascular Unit, St. Mary's Hospital Medical School, London, UK*

Although elastic compression stockings produce symptomatic relief, their haemodynamic effects are unknown Air-plethysmography has been used to measure venous volume (VV), venous filling index (VFI), which is a measure of venous reflux, ejection fraction (EF) of the calf muscle pump as a result of one tip-toe movement and the residual volume fraction (RVF) after 10 tip-toe movements[1] Twenty normal limbs and 20 limbs with primary varicose veins (PVV) have been studied Deep venous disease had been excluded by venography, duplex scanning and ambulatory venous pressure (AVP) measurements.

Subsequently, graduated medium compression stockings (30 mmHg at the ankle, 15 mmHg at the calf, 8 mmHg at the thigh) were worn by the patients with PVV for 4 weeks. At the end of this period air-plethysmography and AVP measurements were repeated with the stockings off The results of the measurements (median and 90 per cent range) and the mean percentage change as a result of long-term elastic compression are shown in the *Table.*

Limbs	AVP (mmHg)	VV (ml)	VFI (ml/s)	EF (%)	RVF (%)
Normal		112 (80–150)	1·1 (0·6–1·6)	75 (60–85)	15 (1–30)
PVV before stocking	43 (6–55)	165 (75–331)	6·0 (1·6–15)	54 (38–82)	49 (15–57)
PVV after stocking	33 (6–47)*	156 (76–280)*	4·2 (1·5–12)*	61 (49–86)*	36 (6–49)*
Percentage change	−16	−5·5	−15	+21	−27

* $P<0·01$, Wilcoxon test for paired samples

The results indicate that elastic compression produces a long-term haemodynamic benefit The decrease in AVP is the result of reduction in venous reflux and an increased ejecting capacity of the calf muscle pump.

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Splenic reticuloendothelial function following surgery

M.C. Aldridge, S. Cheslyn-Curtis, S.J.D. Chadwick and H.A F. Dudley, *Academic Surgical Unit, St. Mary's Hospital, London, UK*

Although the spleen is a major component of the reticuloendothelial system, with an important role in filtering blood-borne particles, the effects of surgery on splenic function or on resistance to Gram-negative infection are incompletely understood.

Kupffer cell extraction of technetium tin colloid (TTC) was measured in preoperative (group A; $n=20$) and postoperative patients (11 uncomplicated, group B; nine critically ill, group C). Eight (two group B, six group C) had also undergone splenectomy $T_{\frac{1}{2}}$ blood clearance (min; mean ± s.e.m.) was 1·47 ± 0·08 (group A), 2·22 ± 0·21 (group B) ($P<0·01$), 2·46 ± 0·18 (group C) ($P<0·001$).

The effect of splenectomy on the clearance kinetics of TTC and of ^{75}Se-labelled *Escherichia coli* was also studied in rabbits 1 month after either sham laparotomy or splenectomy (see *Table*).

	Sham laparotomy ($n=6$)	Splenectomy ($n=7$)
$T_{\frac{1}{2}}$ TTC (min)	0·69 ± 0·07	1·01 ± 0·06*
$T_{\frac{1}{2}}$ *E. coli* (min)	0·68 ± 0·02	1·12 ± 0·11*
Uptake as percentage of injected dose/g of tissue		
Liver uptake (TTC)	0·70 ± 0·07	0·51 ± 0·02*
Liver uptake (*E coli*)	0·65 ± 0·06	0·49 ± 0·03*
Lung uptake (TTC)	0·23 ± 0·10	0·51 ± 0·14*
Lung uptake (*E coli*)	0·23 ± 0·04	0·40 ± 0·08*

Data are mean ± s.e.m., * $P<0·05$ (Mann–Whitney U test)

These results suggest that there is impairment of reticuloendothelial function after surgery which can be detected in patients by delayed clearance of TTC, and that splenectomy reduces Kupffer cell uptake of both TTC and *E. coli* with a consequent increase in pulmonary localization We conclude that the spleen is important for normal Kupffer cell clearance of particulate matter following surgery, thus supporting the concept of splenic preservation.

Lymphocyte traffic in rat small bowel transplants

P.A. Lear, A. Cunningham, P.W. Crane and R.F.M. Wood, *Department of Surgery, St. Bartholomew's Hospital, London, UK*

Small bowel transplants incite not only a vigorous rejection response but also induce graft-versus-host disease. To elucidate these phenomena, the lymphocyte traffic of host and donor origin has been discretely monitored in unimmunosuppressed (control) and cyclosporin-treated (15 mg kg^{-1} day^{-1} for 7 days) DA recipients of PVG intestinal transplants. PVG small bowel grafts are rejected in 6–8 days by untreated DA hosts but survive more than 50 days after cyclosporin therapy. Unimmunosuppressed rats were killed on days 1 to 6, cyclosporin-treated rats on days 7, 14, 21 and 28. All host lymphoid tissues and grafts were harvested and stained with strain-specific monoclonal antibodies to identify cells of host and graft origin (MN4 – anti-class 1 DA; OX27—anti-class 1 PVG).

When graft infiltration was assessed in control animals, host lymphocytes were found particularly in the Peyer's patches on day 1. Later there was progressive infiltration of the lamina propria and finally the epithelium, which was mostly destroyed by day 6. In cyclosporin-treated animals, the architecture of the gut remained normal throughout, except the Peyer's patches which were replaced by simple accumulations of host lymphocytes. Epithelial lymphocytes were also of host origin.

Assessment of host infiltration showed that in control animals all host lymphoid tissues contained graft-derived cells from day 1. The number of cells increased until day 4 after which they disappeared, presumably destroyed. In contrast, on day 7, cyclosporin-treated rats had very large numbers (5–10 times that of controls) of graft-derived cells in all lymphoid compartments. They increased further on day 14, but were absent from all areas except the thymus by day 28. These studies demonstrate the true traffic of 'passenger leucocytes', and give some insight into the origins of graft-versus-host disease.

Pulsatility of insulin and glucagon secretion from intraportal and intrasplenic islet autografts in Cynomolgus macaques

R. Sutton, D.R. Matthews, M. Burnett, D.W.R. Gray, R.C. Turner and P.J. Morris, *Nuffield Department of Surgery and Diabetes Research Laboratories, Oxford University, Oxford, UK*

Both insulin and glucagon are normally secreted in a regularly pulsatile manner, maximizing the efficiency of normal glucose homeostasis, however, the pancreatic endocrine pacemaker remains unidentified[1]. Pulsatility of insulin and glucagon release were examined in 11 normal animals and six animals after total pancreatectomy and subsequent islet autotransplantation. Fasting blood samples were taken at 2-minute intervals over 1 h, and plasma glucose, insulin and glucagon were determined. Time series analysis was performed by autocorrelation with Fisher's Z transformation, and by Fourier transform analysis.

Significant positive insulin peaks were present on autocorrelation of data from four normal animals, three out of four animals with well-maintained graft function (two intraportal and one intrasplenic), and neither of two animals with late graft failure. Pooled data from normal animals showed peak oscillatory activity at 14 min, pooled data from transplanted animals showed peak oscillatory activity at 24 min on autocorrelation ($r = 0.251$, $P < 0.05$), although there was no unified peak on Fourier analysis.

These data suggest that pulsatile hormone release may occur from an islet graft, and may contribute to more efficient glucose homeostasis. In addition, the pancreatic neural network would appear more likely to modulate than initiate pulsatile islet hormone secretion.

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An objective approach to maintenance therapy in renal transplantation

C.S. Ubhi, F.T. Lam, A.I.D. Mavor and G.R. Giles, *Department of Surgery, St. James's University Hospital, Leeds, UK*

Renal allograft recipients immunosuppressed with cyclosporin alone who are likely to require additional maintenance therapy may be identified by fine needle aspiration cytology (FNAC)[1]. In this prospective study we question the benefits of earlier introduction of additional maintenance therapy and whether steroids could be avoided by FNAC monitoring.

Sixty-two recipients of cadaveric renal allografts were monitored by FNAC during the first 30 days after transplantation. Nineteen patients displayed no sign of rejection (group A), 24 patients had apparent resolution of rejection by intravenous methylprednisolone (group B), whereas 19 had evidence of continuing rejection (group C) after three doses of methylprednisolone. Group C patients were randomized to receive maintenance doses of either azathioprine or oral prednisolone.

Assessment at 3 months showed the median (range) of serum creatinine for groups A, B and C to be 139 (104–206), 148 (110–450) and 205 (83–324) μmol/l respectively. Eighteen of the 19 group A patients were rejection-free on cyclosporin alone. Only five group B patients have required oral prednisolone after further rejection episodes whereas seven group C patients commenced triple therapy. There were three graft losses in group C and two in group B ($P > 0.05$ Fisher's exact test).

We have demonstrated that FNAC provides an objective approach to maintenance immunosuppression in patients experiencing early rejection episodes and that oral steroids may be avoided in 65 per cent of patients.

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Soluble interleukin 2 receptor levels in renal allograft dysfunction

J.L.R. Forsythe, B.K. Shenton, N.R. Parrott, R.M.R. Taylor and G. Proud, *Department of Surgery, University of Newcastle upon Tyne, UK*

T-lymphocyte activation is associated with increased expression of interleukin 2 receptor (IL-2r), both on the cell and in the free soluble form. The hypothesis that soluble IL-2r levels may rise during renal allograft rejection was tested.

Initially, IL-2r levels, as measured by an enzyme-linked immunosorbent assay, were determined in five normal volunteers and 10 renal transplant recipients (five with stable function and five suffering rejection). Levels in the three groups were significantly different.

	Normals	Stable	Rejection
Number of subjects	5	5	5
Median IL-2r level (units/ml)	244	960	1605
Significant difference from rejection (Mann–Whitney *U* test)	$P = 0.008$	$P = 0.03$	—

Daily plasma samples were then collected from renal allograft recipients in the first 14 days after transplantation. Out of 152 assays now performed, a plasma level over 1900 units/ml ($n = 18$), was always associated with rejection and a rise of over 400 units/ml in 24 h ($n = 6$) only occurred before a diagnosis of rejection. On no occasion was subsequently proved rejection seen in the face of low and stable IL-2r levels.

Plasma IL-2r levels do rise during allograft rejection and this fact may be of great diagnostic value in allograft dysfunction.

A clinical evaluation of a new preservation solution: phosphate-buffered sucrose

F.T. Lam, C.S. Ubhi, A.I.D. Mavor, J.P.A. Lodge and G.R. Giles, *Department of Surgery, St. James's University Hospital, Leeds, UK*

Short-term preservation of human kidneys is mainly conducted by perfusion with hyperosmolar citrate. This is associated with a relatively low primary function rate. We have tested an alternative solution in our clinical transplant programme. Kidneys from 18 consecutive donors were alternatively allocated to *in situ* aortic perfusion with hyperosmolar citrate or phosphate–buffered sucrose. The age, renal function, histocompatibility antigen match, and warm and cold ischaemic times proved similar in both groups. Twenty-five kidneys were transplanted locally and immunosuppression was initially by cyclosporin alone. The mean preservation time for both groups was 19 h.

Primary function was seen in nine kidneys (50 per cent) perfused with citrate and 15 (84 per cent) with sucrose ($P = 0{\cdot}037$ Fisher's exact test). A comparison between kidneys with primary function showed no significant difference in the 24-h urine output; however, the serum creatinine by the seventh day was significantly lower in the sucrose group ($P = 0{\cdot}029$ Mann–Whitney U test). Inulin clearance on day 1 was significantly better with sucrose ($P = 0{\cdot}01$ Mann–Whitney U test)

It is concluded that the use of phosphate-buffered sucrose is associated with a higher rate of primary graft function and an improved renal clearance.

Announcement

Reviews

The Editorial Board of *The British Journal of Surgery* continues to invite review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium of £100. Potential authors seeking advice on the suitability of review topics are advised to contact: Professor D. C. Carter, Regius Professor of Clinical Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK

Leading articles

The Editors invite submissions of signed leading articles to *The British Journal of Surgery*. These articles should be 600–1000 words in length, should address controversial topics of current interest and should be supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium of £100 is payable on publication. Potential authors seeking advice on the suitability of topics are advised to contact: Professor D. C. Carter, Regius Professor of Clinical Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Surgical workshops

The Editors invite the submission of articles describing technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they can be accompanied by no more than two figures but should not carry supporting references. Articles submitted to the Surgical Workshop series may be subjected to external review and assessment by the Editorial Board before acceptance.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is likely to be high. Authors are advised to restrict such reports to a maximum of 500 words, to use no more than five references and to submit no more than one illustration.

Correspondence

Early cholecystectomy after sphincterotomy for common duct lithiasis

Sir

We were very interested to read the article by Worthley and Toouli (*Br J Surg* 1988; **75**. 796–8), and Martin and Tweedle's letter (*Br J Surg* 1989, **76**: 101)

Worthley and Toouli state that gallbladder non-filling during endoscopic retrograde cholangiopancreatography (ERCP) is a predictive factor of biliary complications that justify cholecystectomy This idea seems to be disputed by Martin and Tweedle. We performed early and systematic cholecystectomy on elderly or very elderly surgical patients (over 75, average age 83 years) who had undergone sphincterotomy for common duct lithiasis[1].

We have therefore retrospectively assessed our current data 36 consecutive patients were treated in this way The ERCP, performed by the same practitioner, filled the gallbladder in 26 cases (group I) and did not fill it in nine cases (group II)

The percentage of acute cholecystitis (histological result given by the same laboratory) was 65 per cent (17 of 26 patients) for group I and 55 per cent (five of nine patients) for group II. No statistical difference was observed between the two groups

For our patients, gallbladder non-filling during ERCP is not a predictive factor of gallbladder problems.

J. J. Duron
P. Imbaud
J. L. Dumont
J. Validire

Hôpital Jean Rostand
94200 Ivry
France

1. Duron JJ, Roux JM, Imbaud P, Dumont JL, Dutet D, Validire J Biliary lithiasis in the over seventy-five age group a new therapeutic strategy *Br J Surg* 1987, **74** 848–9.

For debate: cancer of the colon

Letter 1

Sir

We read Mr Marston's paper (*Br J Surg* 1989, **76** 71) with interest and, indeed, others have also considered a role for subtotal colectomy in the management of colon carcinoma[1] Many of Mr Marston's arguments make very good sense.

The more widespread use of the flexible sigmoidoscope suggests yet another alternative. When performing a left-sided resection, why not tailor it to leave about 60 cm of colon *in situ*, this length being accessible subsequently to the flexible instrument? The latter is more appropriate as a screening instrument than the colonoscope in that only simple patient preparation is required and it can be performed by the non-specialist in the outpatient department[2], all the more easily since the sigmoid colon and splenic flexure do not then present a problem.

E. J. Gibney

Beaumont Hospital
Dublin 9
Eire

1. Brief DK, Brener BJ, Goldenkranz R, Alpert J, Yalof I, Parsonnet V An argument for increased use of subtotal colectomy in the management of carcinoma of the colon. *Am Surg* 1983; **49** 66–72
2. Neugut AI, Pita S. Role of sigmoidoscopy in screening for colorectal cancer: a critical review *Gastroenterology* 1988, **95**: 492–9

Letter 2

Sir

I was interested to read Mr Marston's paper debating the case against total colectomy as a standard treatment for cancer of the colon (*Br J Surg* 1989; **76**. 71)

Mr Marston is, as always, stimulating and his arguments most plausible. His second point, however, states that there is ‘a high incidence of recurrent colonic cancer following partial colectomy because of synchronous or metachronous tumours . ’ When Sir Hugh Lockhart-Mummery and I reviewed the St. Mark's figures[1], we found that the actual incidence of metachronous cancer in those patients cured of one cancer was only 3·5 per cent with a lifelong follow-up Furthermore, the suggestion that removal of the entire mucosal field would eliminate the problem is not true because rectal carcinoma after colectomy is somewhat more common than a second colonic carcinoma and thus would still dictate a need for follow-up and sigmoidoscopy. Furthermore, there is no evidence that removal of the entire colon would eliminate suture-line recurrence which is most commonly because of extra visceral residues of the primary tumour or implantation of viable tumour cells Neither of these would be eliminated by total colectomy. Improvements in colonoscopic surveillance and polypectomy have further reduced the argument for total colectomy since the 1970s when our papers on the subject were written. We argued then that each primary cancer should be treated on its merits, that no colorectal cancer should be removed without proper visualization of the entire colon and rectum (to eliminate missed synchronous tumours), and that 3-yearly postoperative surveillance for life was probably worthwhile.

I believe that these arguments hold good today.

R. J. Heald

Basingstoke District Hospital
Basingstoke RG24 9NA
UK

1 Heald RJ, Lockhart-Mummery HE. The lesson of the second cancer of the large bowel *Br J Surg* 1972, **59** 16–19.

Facial paralysis due to a benign parotid tumour

Sir

We were interested to read the paper by Whillis, Goepel and Shorthouse (*Br J Surg* 1989; **76**. 95) reporting a case of a Warthin's tumour presenting with a parotid swelling and paresis of the ipsilateral facial nerve A review of the literature by the authors found only six cases of benign parotid tumours causing facial nerve paresis. Only one other case was due to a Warthin's tumour

We would suggest that this condition is more common than has been thought Two similar cases of benign parotid tumour with ipsilateral facial nerve paresis presented in 1988

The first, a 67-year-old man, presented with a 7-week history of a right-sided facial nerve palsy affecting all but the temporal branches of the nerve There was an associated right-sided parotid swelling which had been present for some years. The swelling was soft and painless, but there was some suggestion that it had recently enlarged

A superficial parotidectomy was performed and the patient made an excellent postoperative recovery. Three months later his facial nerve paresis had almost completely resolved Histology subsequently reported an adenolymphoma (Warthin's tumour) with no evidence of malignancy

The second patient was a 34-year-old woman who presented with a 2-month history of left facial paresis associated with a parotid mass which had been present for 3 months CT scan confirmed a deep parotid tumour. ACTH was administered and some nerve function was regained before surgery Parotidectomy was performed for a pleomorphic adenoma. The facial nerve was preserved with the exception of the cervical branch which was enmeshed in the tumour. The resected branch was immediately repaired by nerve graft

Three months after surgery complete resolution of the paresis had occurred with the exception of some residual weakness in the distribution of the cervical branch

These two patients, together with the previous report, highlight the requirement to judge each case on its merits, it can no longer be said that facial nerve involvement is ‘proof positive’ of malignancy in parotid swellings.

N. B. Corner
S. M. Allan
R. M. Heddle
P. J. Pheils

Kent and Canterbury District Hospital
Canterbury CT1 1NG
UK

Heller's myotomy

Sir

Crookes, Wilkinson and Johnston (*Br J Surg* 1989; **76** 99–100) are to be commended on their attempts to ensure competency of the cardia after a modified Heller's myotomy for achalasia Their careful follow-up with the absence of heartburn in any of their patients postoperatively and the documentation of normal oesophageal acid exposure in five of six patients on 24-h pH monitoring gives objectivity to their conclusion. The debate over the need for reflux protection after a Heller's myotomy has gone on for many years and there have been a number of alternative solutions proposed. As the authors point out, by limiting the myotomy to the oesophagus, Ellis and co-workers claim an absence of gastro-oesophageal reflux[1]. However, their impression is not supported by pH monitoring Although Crookes *et al.* have described what they consider is a novel approach there have been two previously described partial fundoplications that have been specifically designed to be used during a Heller's myotomy. The first is the Dor procedure in which a flap of gastric fundus is laid anteriorly over the myotomy, with interrupted suture of the flap to the edges of the myotomy[2]. This method applies the partial wrap to the area that would have been left open by the operation described by Crookes *et al*

The second partial fundoplication is that described in 1963 by Toupet[3] in which a posterior wrap of very similar dimensions was applied to the oesophagus in a similar fashion to that described by Crookes *et al.*, both as a primary anti-reflux operation and also for anti-reflux protection after a Heller's myotomy. Currently a partial wrap is to be preferred because the aim of surgery in achalasia is to reduce the outflow resistance of the oesophagus to allow food and liquid to pass through by the effect of gravity and any anti-reflux procedure must not add to that resistance.

In our opinion the Dor procedure is to be preferred because it has the advantage that the wrap is applied to the area in which the sphincter defect has been created, thus transmitting the changes in intra-abdominal pressure directly to the mucosa of the lower oesophagus. It also protects the exposed area of mucosa. It achieves the same effect as the Toupet or Crookes procedure in maintaining the separation of the myotomized muscle and can be performed without circumferential dissection of the lower oesophagus

The most extensive publication of this procedure in the English language is that of Csendes who has recently described a series of 100 consecutive Heller procedures with the Dor type of reflux protection[4]. He documented an absence of reflux symptoms in all except one patient and demonstrated a positive standard acid reflux test in 19 per cent, a similar figure to that reported by Crookes.

While commending the report of Crookes *et al*, we would suggest that the Dor procedure is simpler and safer while being equally effective.

S. E. A. Attwood
G. Zaninotto

Creighton University
Omaha
Nebraska 68131
USA

1. Ellis FH, Crozier RF, Watkins E Operation for esophageal achalasia. results of esophagomyotomy without an antireflux operation *J Thorac Cardiovasc Surg* 1984, **88**. 344–51.
2. Dor J, Humbert P, Paoli JM *et al.* Traitement du reflux par la technique dite de Heller-Nissen modifiee *Presse Med* 1967, **75**. 2563–5.
3. Toupet A. Technique d'oesophago-gastroplastie avec phreno-gastropexie appliquee dans la cure radicale des hernies hiatales et comme complement de l'operation de Heller dans les cardiospasmes. *Acad Chir* 1963; **89**. 394–401
4. Csendes A, Velasco N, Braghetto I, Henriquez A. Late subjective and objective evaluation of the results of esophagomyotomy in 100 patients with achalasia of the esophagus *Surgery* 1988; **104**· 469–75

Acute lower limb ischaemia

Sir

We read with interest the article by Walker and Giddings (*Br J Surg* 1988; **75** 1189–92) concerning the use of streptokinase and surgery in the treatment of acute lower limb ischaemia However, we feel that there are several points that require clarification

In order to allow comparison between this series and others reported in the literature, it is important to know what exclusion criteria are used. Specifically, did they exclude all patients with a previous history of cerebrovascular accident or only those with a recent history of less than 2 months[1]? Similarly, did they exclude patients older than 75 years (listed as a relative minor contraindication in the NIH criteria[1])? They state that 56 patients with subacute ischaemia were treated with heparin alone, but do not detail the length and duration of ischaemia or its severity, the ankle pressure and/or ankle·brachial index or whether any tissue necrosis was present. On what grounds were they selected for heparin alone rather than arteriography with a view to thrombolysis or surgery, and what was their outcome?

How many patients were excluded from this study following failure to position the catheter for thrombolysis adequately, and what was their outcome?

In their discussion, it is suggested that proximal stenoses should be dilated first and then the distal thrombus perfused, with the catheter presumably lying within the dilated 'thrombogenic area'. How many patients required this technique and how often did this area require thrombolysis itself before the catheter could be safely withdrawn?

Finally, the authors inadvertently included a case of brachial occlusion in this article However, this is another interesting application for low-dose intra-arterial thrombolysis and therefore we would appreciate a few more details. Which approach did the authors use and what was the aetiology of the lesion?

D. C. Berridge
R. H. S. Gregson

University Hospital
Nottingham NG7 2UH
UK

1 Thrombolytic therapy in thrombosis· a National Institutes of Health Consensus Development Conference *Ann Int Med* 1980; **93**. 141–4.

Authors' reply

Sir

We are pleased to reply to the comments of Mr Berridge and Dr Gregson.

We excluded patients who had suffered a cerebrovascular accident within the previous 2 months and those who had had surgery within the previous 3 weeks, but not patients greater than 75 years of age. As stated in our protocol, all patients had ischaemia of greater than 12 h duration and all of those treated with heparin alone had already undergone diagnostic arteriography, which we regard as essential before a choice of treatment is made. As the protocol states, patients with calf muscle necrosis were treated by primary amputation One patient with a blocked femoropopliteal graft could not be given the infusion because the catheter could not be passed into the strictured origin of the graft and this patient was managed surgically. The number of proximal dilatations was not separately recorded but some required exit thrombolysis and no complication ensued The case of brachial occlusion was from our first series and was due to cardiac embolus The catheter was passed from the groin. We do not have sufficient experience of this technique in the upper limb to suggest a protocol at present.

W. J. Walker
A. E. B. Giddings

Royal Surrey County Hospital
Guildford GU2 5XX
UK

Incisional hernia

Author's reply

Sir

Mr A E Kark (*Br J Surg* 1989; **76** 104) needs only to look back at page 59 of the same volume to find that you discourage the provision of references in 'Surgical workshops'. There are important differences (*Br J Surg* 1988, 75: 1149) between Boerema and the paper to which he refers, but he would first have to be able to understand the difference between a Bassini and a Shouldice How relevant is his statement that nylon sutures do not eliminate infection when those recommended are absorbable, or his reference to skin infection when the method described (not Boerema's) has virtually eliminated it? Who is going to try Boerema's operation if a vociferous protagonist admits to serious skin infections but persists 38 times to discover this, and does not recommend dieting as an important preliminary to operation in the obese?

Cognoscenti of the literature on the treatment of incisional hernia will recall the dismal but honestly reported results from a British centre of excellence which shall remain nameless. There is no room for complacency. Boerema's operation has not entered British texts and should not do so

F. Weale

Gravesend and North Kent Hospital
Gravesend DA11 0DG
UK

Growth rates in hepatic metastases

Authors' reply

Sir

We would like to thank Messrs Pritchett and Coleman (*Br J Surg* 1989; **76**. 206) for their interest in our paper 'Growth rates in hepatic metastases' (*Br J Surg* 1988; **75**· 641–4) They have correctly identified a proofreading error which resulted in a plus sign missing from the volume formula While we accept the comment 'that a volume formula should contain three length dimensions', this was not possible in our study because the 'slicing' distance of the CT scanner used was insufficiently narrow to give a meaningful third dimension. We did, however, make the observation that small metastases were sausage-shaped and not spherical, hence our selection of formula

In response to the second question, there was no arbitrary selection of data points. When only two points were used for analysis it was because the other scans were indistinct. When more than two scans were utilized, a linear regression analysis was employed

The present study was not designed to test the hypothesis 'that human colorectal carcinoma exhibits Gompertzian growth'. This would require several scans on many metastases in individual patients. It may be of interest, however, that we now have three patients who have had five or more scans studying several metastases, and it would appear that Gompertzian growth kinetics most closely fit the observed pattern of growth

The correlation coefficient value is +0·91. We concede that if the single data point referred to was removed then the statistical analysis would be different. We also accept that there may be an argument for removing it, but it was for this reason that we chose to present all the data, tedious as it may seem, in tabular form. The reader could then draw his own conclusions.

We believe that this, however, is peripheral to the message that we wish to present Messrs Pritchett and Coleman are entirely correct when they say that the distinction between overt and occult metastases is artificial We used the term 'occult' to indicate metastases which were not recognized by the surgeon but were identified by other techniques. This had an important implication for our understanding of the natural history of the disease, because when we first used the term it was thought that deaths after curative surgery were due to venous dissemination of neoplastic emboli at the time of laparotomy Clearly very small tumour deposits on the liver surface might be detected by the surgeon as 'overt' metastases, while large deposits deep in the substance of the liver might be missed but detected by CT or intraoperative ultrasound as 'occult' metastases Hence any distinction between 'occult' and 'overt' is artificial

The message in the present paper is a simple one Recent studies show that few patients who do not have 'occult' metastases demonstrated by CT at the time of surgery or intraoperative ultrasound subsequently die from the disease If these 'occult' and 'overt' metastases are in most cases at least 1 cm in diameter at that time, then the metastatic process must have taken place long before the patient became symptomatic. Indeed, careful consideration of the data might suggest that colorectal cancer behaves consistently as a metastasizing or non-metastasizing variant from an early stage in the natural history

I. G. Finlay
C. S. McArdle

Royal Infirmary
Glasgow G4 0SF
UK

Suction drains

Sir

The method for securing suction drains described by Stacey-Clear and Heddle (*Br J Surg* 1988, **75**· 1195) is not new We have been using this method routinely for more than 20 years We believe it was first described by the late Mr F N. Cort, who showed it to us

Our technique differs slightly from that described in their paper. A small length of the end of the suction drain tubing is cut off from the end of the drain. The drain is then placed in the wound with a loop of skin suture through the end hole of the suction drain tubing The suture is then passed through the small separate piece of suction drain tubing and is tied loosely with the piece acting as a bridge on the skin surface. This not only prevents the suture from being tied too tightly, but identifies it to the nursing staff who can recognize it easily when it comes to removal of the drain

We use this method routinely in the securing of all suction drains, except following thyroid and parathyroid surgery where the tip of the drain lies deep to the strap muscles We have found it to be very successful and recommend it for general use.

D. A. Ratliff
A. D. Barnes

The Queen Elizabeth Hospital
Birmingham B15 2TH
UK

Ceruletide and management of retained common bile duct stones

Sir

There is at present only limited published data on the value of ceruletide in the management of retained common bile duct stones. We were therefore surprised that Dr Tritapepe and colleagues (*Br J Surg* 1988, **75**. 144–6) did not mention the Liverpool experience of this technique in their discussion[1]. We would agree that this method of stone removal is safe and theoretically attractive, but we were disappointed with its use in practice. Using the same dose of ceruletide and similar volumes of saline infusion as those described by Professor Cuschieri[2], we were only successful in removing small stones (less than 8 mm) from three of ten patients. These results are probably no better than might have been achieved had we used saline infusion alone It is worth remembering when evaluating this or similar methods of stone removal that a number of common duct stones are able to pass on their own The addition of mono-octanoin to dissolve stones partially before repeat administration of ceruletide and saline is interesting but the whole appeal of this technique, namely its simplicity, is thereby rather lost

S. J. Walker
C. R. Mackie

University of Liverpool
Liverpool L69 3BX
UK

1. Walker SJ, Mackie CR, Mendelson RM, Arnold A, Colmer MR Ceruletide for retained biliary stones *Br Med J* 1986, **293**. 595–6
2 Cuschieri A Management of retained biliary calculi relaxation of sphincter induced by ceruletide *Br Med J* 1984, **289** 1582.

Variceal haemorrhage

Sir

We think Mr Jenkins and Professor Shields (*Br J Surg* 1989, **76**: 49–51) do emergency oesophageal transection a disservice when they conclude that it is of little use in patients whose bleeding cannot be controlled by conservative measures, and that good results can only be expected in patients with good liver function In their review of a 'planned management policy' it is clear that all their patients had sclerotherapy and transection was used as a last resort in patients whose bleeding could not be controlled by injection It is not stated how many sessions of variceal injection or number of episodes of rebleeding constituted 'failure of sclerotherapy'

Terblanche's group[1] has shown that the use of three injection sessions to control bleeding during the same hospital admission results in nearly 100 per cent mortality They recommend a maximum of two sessions and if bleeding continues transection or other surgery.

In our prospective randomized study of emergency oesophageal transection *versus* injection sclerotherapy in patients with cirrhosis who had failed conservative measures for control of bleeding (over half were Pugh's grade C), we found no difference in mortality between the two techniques and also concluded that no more than two sessions of emergency injections should be used to control bleeding[2]. In addition we found that transection was better in controlling bleeding Two other randomized studies not cited by Mr Jenkins and Professor Shields also conclude that transection has a role Huizinga *et al.*[3] found that transection was superior to sclerotherapy in controlling bleeding with a similar mortality rate Teres *et al*[4] found that transection was preferable to portacaval shunt in well-compensated cirrhotics In decompensated cirrhotics survival was similar to those receiving sclerotherapy, despite a 71 per cent rate for control of bleeding with transection—the lowest recorded in the literature.

We would suggest that emergency oesophageal transection does have a part to play in the management of patients with bleeding oesophageal varices, but that it must be employed early in the management It should be used either *ab initio* or after a maximum of two attempts at sclerotherapy have failed. To continue sclerotherapy beyond this is to court disaster.

Emergency oesophageal transection is a valuable and viable technique but must be used at the right time

A. K. Burroughs
G. Hamilton
K. E. F. Hobbs

Royal Free Hospital School of Medicine
London NW3 2QG
UK

1. Bornman PC, Terblanche J, Kahn D *et al* Limitations of multiple injection sclerotherapy sessions for acute variceal bleeding *S Afr Med J* 1986, 70: 34–6.
2. Burroughs AK, McCormick PA, Mezzanotte G *et al.* Randomised trial of acute sclerotherapy versus oesophageal staple transection. *Gut* 1988; **29** A739
3. Huizinga WKJ, Angorn IB, Baker LW Esophageal transection versus injection sclerotherapy in the management of bleeding esophageal varices in patients at high risk *Surg Gynecol Obstet* 1985; **160**. 539–46.
4. Teres J, Baroni R, Bordas JM *et al* Randomized trial of portacaval shunt, stapling transection and endoscopic sclerotherapy in uncontrolled variceal bleeding. *J Hepatol* 1987, 4: 159–67

Authors' reply

Sir

Thank you for letting us have an opportunity to reply to the letter from Dr Burroughs, Mr Hamilton and Professor Hobbs in response to our article We fear that the correspondents have missed the point of our article. We did not seek to condemn oesophageal transection and indeed advocate its use in certain circumstances The purpose of our paper, which we described in the introduction and repeated in the discussion, was to emphasize that if the operation was reserved to a late stage in a sequential management policy and therefore carried out only after the patient had been bleeding for some time, the results would be poor Indeed, we advocated that surgical treatment should be instituted as early as possible to prevent the deterioration associated with prolonged conservative management. Our current practice is that if the bleeding continues despite two sessions of adequate sclerotherapy, plus adjuvant treatment including somatostatin and balloon tamponade, we have recourse to operation.

We did not refer in detail to their prospective randomized trial comparing emergency oesophageal transection and injection sclerotherapy in cirrhotics, because, as far as we are aware, it has been published in abstract form only and thus defies detailed analysis. The authors, however, cannot be seriously advocating that every patient admitted with an acute variceal haemorrhage should be considered equally for oesophageal transection or injection sclerotherapy. An operation of this magnitude should only be carried out as initial treatment if there are reliable predictors of recurrent haemorrhage, but, sadly, these are often lacking

We have re-read the article by Huizinga, Angorn and Baker[1] and cannot reconcile the 87.5 per cent mortality rate which they report, when the operation is performed in emergency circumstances, with the sentence in the above letter There is a whole world of difference in outcome, when operation for oesophageal varices is carried out in an emergency, compared with elective circumstances Moreover, in the paper by Teres *et al.* it is difficult to determine what was emergency and what was elective treatment, for '80 per cent of patients were 'randomized' at the time of variceal bleeding within 3 weeks of hospital admission for variceal bleeding'. This definition of emergency treatment of acute variceal bleeding is considerably different from ours and, we assert, most others working in this field

Emergency oesophageal transection is a valuable technique, which we emphasized on several occasions in our paper Timing, however, is of the essence and we cannot accept that it should be considered equally with injection sclerotherapy as the very first treatment to be carried out when the patient is admitted to hospital. We believe that most gastroenterologists would agree with this view until clear predictors of recurrent haemorrhage are identified.

R. Shields
S. A. Jenkins

The University of Liverpool
Liverpool L69 3BX
UK

1. Huizinga WKJ, Angorn IB, Baker LW. Esophageal transection versus injection sclerotherapy in the management of bleeding esophageal varices in patients at high risk *Surg Gynecol Obstet* 1985; **160**: 539–46.

Preoperative cardiac risk of aortic aneurysm surgery

Sir

We read with interest the paper by Fletcher *et al.* on the risk of aneurysm surgery as assessed by preoperative gated heart pool scan (*Br J Surg* 1989; **76**: 26–8) We, like the authors, concur that left ventricular ejection fraction (LVEF) is an accurate preoperative risk predictor of postoperative cardiac complications[1] However, despite their assessment of risk, three patients with LVEF of greater than 45 per cent developed postoperative congestive cardiac failure We feel that this figure is unacceptably high. The authors also state that, owing to pressure on intensive care beds, it was not possible to use preoperative pulmonary artery catheterization routinely

We have previously shown that all patients undergoing abdominal aortic surgery do not require pulmonary artery catheterization[2]. It has been our policy at The Wellesley Hospital to measure LVEF on all patients undergoing such surgery routinely. Patients with LVEF of less than 50 per cent are selected for pulmonary artery catheterization Catheters are inserted on the morning of surgery and Starling curves are constructed. Based on this derived haemodynamic data, optimal cardiac performance is maintained throughout. In a series of 66 consecutive patients, postoperative cardiac complications occurred only in patients with LVEF of less than or equal to 30 per cent

We feel that all patients undergoing abdominal aortic surgery should have preoperative assessment of left ventricular function by radionuclide means. Once the high-risk patient has been successfully isolated, optimal cardiac performance must be maintained throughout the perioperative period. This high-risk group should not be denied the benefit of perioprative central haemodynamic monitoring

W. P. Joyce

The Wellesley Hospital
Toronto M4Y 1J3
Canada

1 Joyce WP, Provan JL, Ameli FM, McEwan P. Radionuclide angiography at rest and during exercise in predicting outcome in patients undergoing abdominal aortic reconstructive surgery *Can J Surg* 1987, **30**: 305
2 Joyce WP, Provan JL, Ameli FM, McEwan P, Jelenich S, Jones DP. Do all patients undergoing abdominal aortic surgery require central haemodynamic monitoring? *Br J Surg* 1988, **75**: 383

Carotid body tumours

Sir

We read with interest the paper by McPherson *et al.* (*Br J Surg* 1989, **76** 33–6) on their excellent results obtained in treating patients with carotid body tumours and other cervical paragangliomas It is noteworthy that the oldest patient operated on in the series was 61, and the median age for the group was 47 While the morbidity and mortality rates associated with resection of carotid body tumours have decreased in recent years, it is still a hazardous operation in the elderly Although the authors mention the natural history of carotid body tumours, we were surprised that they did not indicate that there may be a role for observation alone in selected cases for this slow growing tumour which rarely metastasizes

Over a 33-year period we have had three patients with carotid body tumours who refused operation and six who were considered unresectable at operation These patients have been followed up for a median

Table 1 *Outcome of patients with untreated carotid body tumours*

Reference	No of patients	Median follow-up	Outcome
Farr[1]*	7	> 10 years	All alive with disease
Krupski *et al* [2]	3	8–10 years	All alive with disease
Lack *et al.*[3]	3	10 years	One patient dead (13 years) from unrelated cause
Shamblin *et al* [4]	13	Not published	All alive with disease
Dickinson *et al.*[5]†	7	Not published	All alive with disease

*One patient lost to follow-up; †three patients lost to follow-up

of 7·5 years (range from 6 months to 15 years) Eight of the nine have stable disease, one has clinical evidence of progression, and all are asymptomatic. This information, combined with that from other series (*Table 1*) has led us to recommend observation alone for these tumours in elderly or high-risk patients

***P. J. O'Dwyer**
D. P. McCabe
P. S. Vaccaro
A. G. James

**University College Dublin*
Dublin 4
Ireland

The Ohio State University Hospital
Columbus
Ohio
USA

1. Farr HW. Carotid body tumours. a thirty year experience at Memorial Hospital *Am J Surg* 1967, **114**. 614–19
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Treatment of cancer of the colon

Sir

In response to the published preference of Mr Marston for a subtotal colectomy and ileorectal anastomosis in every case of colonic cancer (*Br J Surg* 1989; **76**· 71), we wish to emphasize the following points.

1. The maximum published incidence of metachronous tumours is 10·2 per cent[1], and it may be argued that the policy of routine subtotal colectomy involves an unnecessary resection in 90 per cent of these patients.
2. Colonic cancers are maximally distributed in the sigmoid and rectosigmoid junction[2] and therefore many of these may require resection of varying portions of the rectum as well, and thus require more than a subtotal colectomy.
3. Suture line recurrence owing to implantation of exfoliated malignant cells within the lumen is uncommon and, in any event, is unlikely to be influenced by the length of bowel resected[3]. On the other hand, lymphatic and hepatic spread, which chiefly governs the prognosis[4], is certainly not influenced by the extent of resection. Unlike oesophageal cancer, which has documented submucosal spread[5], colon cancer has much less predilection to mucosal and submucosal spread.
4. As extracolonic disease is the problem, these patients cannot be spared 'the expensive and cumbersome process' of tumour marker estimation and other surveillance for tumour recurrence.
5. The quoted figure for anastomotic leakage rate following colocolic anastomosis is 4 1 per cent[6] At our centre, one of 30 patients in the 2 years from 1987 to 1988 had leakage This is sufficiently low to warrant continuation of the procedure
6. In our centre, five of 15 patients operated on in 1988 for colonic cancer were under 40 years What does the author suggest be done if a patient undergoing a right colonic resection at, say, 36 years develops a second malignancy in the rectum, a terminal ileostomy, or an ileal pouch–anal anastomosis?
7. Even in obstructed left colon cancers, the role of subtotal colectomy has been limited by the use of on-table colonic lavage and primary colocolic anastomosis[7].
8. Last, follow-up sigmoidoscopy in patients who have undergone ileorectal anastomy, and who have liquid faeces obscuring the field, is not always an easy task.

In the light of the above, we think that the author, by choosing the option of a subtotal colectomy with ileorectal anastomosis for cancer of the colon, will certainly leave the patient 'loose' but no more likely to be living than had he undergone a conventional colonic resection

H. Ramesh
P. G. Thomas

Deva Matha Hospital
Koothattukulam
Kerala
India

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Amputation for peripheral vascular disease

Sir

We applaud the efforts of Messrs McCollum *et al* (*Br J Surg* 1988; **75**: 1193–4) to reduce the ratio of above-knee to below-knee amputations, but are concerned about the very large numbers of major limb amputations performed over a 15-month period. Furthermore, the ratio of above-knee to below-knee amputation is not only determined by the decisions and skill of the surgical team but also by the state of the leg to start with!

We have shown that vascular reconstruction can reduce the number of lower limb amputations by up to 80 per cent in two separate series conducted in the West Midlands over the last 4 years.

In one hospital the mean major limb amputation rate was 55 per year from 1980 to 1984. Following introduction of an intensive limb salvage policy using proximal and distal vascular reconstruction this rate fell to 11 per year despite 142 critially ischaemic legs being treated in 1985 and 1986.

In the second hospital the mean major limb amputation rate in 1984/85 was 48 per year; after instituting a similar reconstructive policy the major limb amputation rate for 12 months in 1987/88 was 16 out of 71 critically ischaemic legs which presented for treatment

Data collected from these studies shows that the rehabilitation of reconstructed patients is faster, more complete and less expensive than those undergoing major limb amputations. It is clearly necessary to train more vascular surgeons in small vessel surgery so that the number of major limb amputations performed for peripheral vascular disease in this country can be drastically reduced.

B. R. Gwynn
C. P. Shearman*
M. H. Sims†

Walsgrave Hospital
**Queen Elizabeth Hospital*
†Selly Oak Hospital
Birmingham
UK

alcifectomy for ductal carcinoma in situ

Sir

The article by Wobbes *et al.* in the February issue of the Journal (*Br J Surg* 1989; **76**: 185–6) discusses the problem of ductal carcinoma *in situ* They state that microcalcifications may be the only sign of the lesion and that the biopsy procedure is aimed at removal of all microcalcifications. If a breast conserving operation is performed, the removal of the microcalcifications with free margins, and confirmation by specimen radiography to verify that microcalcifications have been removed, may be the only procedure necessary. The name of this procedure is microcalcificectomy[1] or calcificectomy (kăl'sĭ-fĭ-sek'tŏ-mi) or simply calcifectomy It is an accurate description of this operation which no doubt will be increasingly performed in the conservative treatment of ductal carcinoma *in situ*.

M. R. Shetty

Northwest Community Hospital
Arlington Heights
llinois 60005
SA

1. Shetty MR (Ed). Microcalcificectomy for Early Breast Cancer. *Northwest Community Hospital Medical Bulletin* 1988; **24** 1.

Breast abscesses

Sir

In their recent correspondence (*Br J Surg* 1989; **76**: 103), Mr Nash and Mr Powles indicate that many non-lactating breast abscesses associated with periductal mastitis are sterile on culture This is incorrect. With appropriate culture techniques, bacteria can be isolated from most, if not all, non-lactating abscesses[1] A combination of cephradine and metronidazole covers the majority of organisms isolated from these lesions.

I agree that breast abscesses can be treated by aspiration combined with appropriate oral antibiotic treatment[2]. It is important to note that in lactating breast abscesses, pus usually reaccumulates and multiple aspirations may be required

J. M. Dixon

The Royal Infirmary
Edinburgh EH3 9YW
UK

1. Bundred NJ, Dixon JM, Lumsden AB *et al.* Are the lesions of duct ectasia sterile? *Br J Surg* 1985, **72**: 844–5.
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Paget's disease

Sir

We read with interest the recent paper by Armitage *et al* (*Br J Surg* 1989, **76**· 60–3). This was a review of eight patients with anal Paget's disease since 1930 They concluded that the association with colorectal tumours may have been exaggerated in previous studies due to confusing Pagetoid spread from an underlying anorectal adenocarcinoma with true Paget's disease.

We agree with Armitage *et al.* as we have treated two cases of anal Paget's over the last 3 years, neither of whom had associated malignancy. The first required an anterior resection for a tubulovillous adenoma which showed mild dysplasia, but there was no evidence of malignancy Both have required local excision of the extramammary Paget's which as yet have been curative.

D. Talbot
T. W. J. Lennard
H. G. Brown
R. M. R. Taylor

University of Newcastle-upon-Tyne
Newcastle-upon-Tyne NE2 4HH
UK

Erratum

'Anastomotic suture materials and implantation metastasis: an experimental study', by J. R. McGregor, D. J. Galloway, P McCulloch and W. D. George, *Br J Surg* 1989; **76**: 331–334, pages 332 and 333, *Tables 1, 2* and *3*. The values for the stainless steel and polypropylene suture materials have been transposed We apologize for this error. The *Tables* should read as follows:

Table 1 *The* in vivo *entrapment and transfer of Mtln3 cells by suture materials*

Suture material	Median number of cells transferred *in vivo*	Range of values
3. Stainless steel	545	141–3371
4. Polypropylene	1197	59–3434

Table 2 *The* in vitro *adherence of Mtln3 cells to suture materials*

Suture material	Median number of cells adhered *in vitro*	Range of values
3. Stainless steel	282	172–861
4. Polypropylene	155	56–662

Table 3 *Radioactivity counts of sutures using free* $Na_2{}^{51}CrO_4$ *solution*

Suture material	*In vivo* study	*In vitro* study
Stainless steel	220 (142–407)	159 (114–337)
Polypropylene	399 (144–698)	144 (97–243)

Book reviews

Amputations and Prostheses. 2nd edition.

M. Vitali. 192 × 260 mm Pp. 217 Illustrated. 1986. London Baillière Tindall. £21 00

The second edition of this book has been extensively updated and makes an excellent contribution to amputation surgery and prosthetics. For too long these subjects have remained isolated from each other and their practitioners are largely ignorant of the problems relating to the other field. If a surgeon routinely carries out amputations without any consultation with those who are responsible for the patients' subsequent rehabilitation then he is out of touch with reality This book underlines the necessity of preoperative consultation and stresses the advantages of such a policy. A good example of this is that preoperative consultation may draw attention to the fact that a patient may be unlikely to walk again and therefore would be better off with a through-knee or Gritti–Stokes amputation rather than the usual above-knee operation. The authors emphasize that patients with bilateral above-knee stumps find it difficult to turn over in bed The quality of the patient's life can be much improved by a more distal amputation.

The opening historical review is full of interesting detail, including reference to the description by Hippocrates of amputation by disarticulation at the knee The famous wooden leg of the Marquis of Anglesey is also mentioned, but a recent comment in Anglesey that the design of artificial legs has not improved much since the early 19th century is omitted for obvious reasons! There follows an illuminating chapter on gait analysis, a subject which is bound to develop in the near future as it is relevant not only to amputees but also to those with neurological problems Prosthetics and individual amputations are exceptionally well described, a good analysis of the advantages and disadvantages of each amputation is given and always with a view to rehabilitation.

There are possibly only two minor criticisms. First, it would have been helpful to have included a fuller description of the skew sagittal flap below-knee amputation with gastrocnemius and soleus muscle myoplasty; second, in the final chapter on future developments, perhaps more could have been made of the importance of having all patients with critically ischaemic limbs seen by vascular surgeons in order to reduce the number of amputations which currently total 5000 each year These are, however, minor criticisms which in no way detract from an excellent book which should be read by all those involved in this branch of surgery. Such study would surely improve the ultimate outcome for these unfortunate customers

I. McColl

Professor of Surgery
Guy's Hospital
London SE1 9RT
UK

Perspectives in Colon and Rectal Surgery

T R. Schrock. 70 × 100 mm. Pp 152 Illustrated 1988 St. Louis Quality Medical Publisher Inc. $193.00

In the Preface, the Editor, Theodore Schrock, states that the originators of the text set out to produce a hybrid of book and journal for colon and rectal surgeons. I am tempted to say that in so doing they have fallen between two 'stools', but I realize that this is a cheap jibe and is not entirely correct The contributors are eminent in their field, and have put together a most readable first edition of a series which hopes to be biannual and topical The articles are crisp and to the point and well laced with the authors' personal experience The latter is refreshing and in a text of this nature is most fitting. The contents are a mixture of review type articles dealing with current topics and more personal viewpoints of difficult management problems or new techniques Although the review articles are excellent, I felt at times that the discussion of several controversial topics was 'thin' and would have benefited by more in-depth appraisal While one appreciates the publisher's desire to reduce the typescript, this could have been achieved by the elimination of the 'sideline' contributions The latter, entitled 'On being an editor or contributor in medical publishing', although most informative, seemed out of place in a book of this nature Hopefully, the next edition will have something a little more relevant in this section.

On balance, this new series of mini-books presents an innovative way of supplying current information about a rapidly expanding speciality. The question the publishers wish to answer is whether I am prepared to buy it. Whereas the content is certainly worthwhile, I coul not justify to my bank manager the purchase of two thin hardback books each year For a text of this length, supplying a limited amount of information, the publishers would be well advised to produce a cheaper 'paperback' version. If they did so, I am sure that it would become a popular addition to the library of most surgeons with an interest in colorectal disease.

N. S. Williams

Professor of Surgery
The London Hospital
London E1 1BB
UK

Diseases of the Veins
Pathology, Diagnosis and Treatment

N. L. Browse, K G. Burnand and M. L. Thomas. 192 × 252 mm. Pp. 67 Illustrated 1988 London Edward Arnold £130 00

The notable advances in phlebology in recent years have not been matched by the availability of major textbooks. This prompts a wider question How does one obtain effective training in phlebology? Rarely does general surgical training provide a proper experience of laboratory tests, specialist radiology and surgical techniques which have lately become part of the management of complex venous disorders Even in most vascular units venous disease tends to receive short shrift, as surgeons seek to stem the rising tide of ischaemic legs and aneurysms Surely if vascular training is to mean anything it should provide a surgeon capable of giving expert care for patients with a range of vascular problems which includes complicated venous and lymphatic diseases. These are more difficult to manage than arterial disease. Of course, primary varicose veins do not demand specialist care, but even here the scope for improved management is immense.

Consider the trainee surgeon, often unsupervised, coming up for air amid the thronged varicose vein clinic, scratching his brow over chronically ulcerated legs or toiling over the venous remnants of the operating list What should be his *vade mecum*? Much has changed since the last edition of that familiar classic from the same stable 'Dodd and Cockett'.

Having established the need, is this book the answer? The aim was to produce 'a practical readable book containing something for medical students, residents and consultants' A modest enough aim, which in the event has been exceeded It begins very well with a canter past the venous milestones in medical literature, beginning in 1550 BC and tactfully reigning in at 1960 It goes on to deal with virtually every venous disorder except portal hypertension, intracranial diseases and piles

The anatomy, physiology, radiology and laboratory methods are authoritatively covered and well illustrated The clinical chapters are rich in practical detail and the references which may number up to 345 per chapter are up-to-date An excellent chapter on pulmonary embolism is contributed by Dr Graham Miller The section on chronic leg ulcers is much enhanced by coloured plates.

A reviewer likes to find something to carp about Why one illustration shows stripping from ankle to groin when the text (rightly in my view) advocates knee to groin was not clear. Perhaps it was part of the authors' attempt to offer a balanced assessment of the options Fortunately this is not too balanced, and the reader is seldom left with uncertainty or indecision (unlike many other large textbooks), for the text is liberally spiced with pithy comments and positive opinions highly relevant to patient care.

My main criticism of this book is its 'utility' presentation which is not up to modern publishing standards and which does less than justice to the text The pages appear somewhat crowded and the visibility of figures and print through the poor quality paper undoubtedly detracts from the quality.

Although many textbooks are to be equally admired for their erudition few are such a positive pleasure to read This book abounds in practical clinical common sense. Both comprehensive and erudite, it escapes the greyness of multiauthorship It cannot fail to be pre-eminent in the field for a long time to come.

C. V. Ruckley

Consultant Surgeon
Royal Infirmary
Edinburgh EH3 9YW
UK

Notices and announcements

19–21 June 1989
Tripartite Meeting
Birmingham, UK
Information Mr Roger Grace, The Royal Hospital, Wolverhampton, UK

26–28 June 1989
Advanced Surgical Techniques Course
London, UK
Information: J. Ashton, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

6–7 July 1989
70th Meeting of the Surgical Research Society
Newcastle upon Tyne, UK
Information. Mr Alan J Rich, Department of Surgery, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne, UK

11–19 July 1989
Cutaneous Malignancy
Glasgow, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

13–15 July 1989
XIVth International Update on Liver Disease
London, UK
Information· Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

21–24 August 1989
4th International Symposium on Obesity Surgery
London, UK
Information. Mr E. R T C Owen, Academic Surgical Unit, The Queen Elizabeth Queen Mother Wing, St. Mary's Hospital, Praed Street, London W2 1NY, UK

27 August–1 September 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Informtion· International Congress and Convention Association, PO Box 50006, Tel Aviv 61500, Israel

7–9 September 1989
Surgical Efficiency and Management Club
Maastricht, Holland
Information. Professor Stig Bengmark, Lunds Universitet, Institutionen for Kirurgi, 221 85 Lund, Holland

10–15 September 1989
3rd International Symposium on Inflammatory Bowel Diseases
Jerusalem, Israel
Information: International Congress and Convention Association, P O. Box 5006, Tel Aviv 61500, Israel

10–15 September 1989
XIV World Congress of Otorhinolaryngology Head and Neck Surgery
Madrid, Spain
Information Technical Exhibit Manager, XIV World Congress of Otorhinolaryngology, C/ Velazquez, 90-5th floor, 28006 Madrid, Spain

11–16 September 1989
33rd World Congress of Surgery
Toronto, Canada
Information: 33rd World Congress of Surgery, Congress Canada, Congress Management, 73 Richmond Street West, Suite 300, Toronto, Canada M5H 1Z4

17–20 September 1989
The Centenary Congress of the Polish Surgical Association
Kraków, Poland
Information: Organizing Committee, ul Kopernika 40, 31-501 Kraków, Poland

17–26 September 1989
Frontiers in Gastroenterology: Colorectal Disease
Birmingham, UK
Information: Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

19–20 September 1989
New Trends in Pelvic Pouch Procedures
Bologna, Italy
Information· R. M. Società di Congressi srl, Via Ciro Menotti 11–20129, Milano, Italy

20–23 September 1989
21st European Pancreatic Club
Glasgow, UK
Information. Mr C. W. Imrie, Consultant Surgeon, Royal Infirmary, Glasgow G4 0SF, UK

21–23 September 1989
Annual General Meeting of the Association of Surgeons in Training
Cardiff, Wales, UK
Information: Mr B Taylor, Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

22–24 September 1989
Association of Colon and Rectal Surgeons of India
Soura Sringar, India
Information. Dr N. A. Wani, Organizing Secretary, Room No 1318, Sher-i-Kashmir Institute of Medical Sciences, Soura Srinagar, India

27 September–1 October 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Information. The Secretariat, 2nd International Conference on Gastrointestinal Cancer, P O. Box 50006, Tel Aviv 61500, Israel

29 September 1989
Progress in Microsurgical Training, Research and Clinical Support. The Sixth Annual Meeting of the Society of Microsurgical Specialists
Buffalo, New York, USA
Information· Elaine Lavigne, University of Vermont, Microsurgical Laboratory, Give Building E-302, Burlington, Vermont 05405, Massachusetts, USA

15–21 October 1989
Recent Advances in Pancreaticobiliary Surgery
Edinburgh, UK
Information. Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

16–20 October 1989
Sixth World Congress on Medical Informatics MEDINFO 89
Beijing, China
Information· Dr Phil R. Manning, Chairman, Scientific Programme Committee, MEDINFO 89, USC School of Medicine, 1975 Zonal Avenue, KAM 317, Los Angeles, California 90033, USA

2–3 November 1989
International Soft Tissue Sarcoma Conference
London, UK
Information: Miss J Mountsteven, Conference Centre, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

15–17 November 1989
Fourth EORTC Symposium on Advances in Gastrointestinal cancer: Research and Treatment
Strasbourg, France
Information. J. P Arnaud MD CMCO, 19 rue Louis Pasteur, Schiltigheim BP 120, 67042 Strasbourg Cedex, France

23–24 November 1989
Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland
Dundee, UK
Information: Mr James Forrester, Department of Surgery, Ninewells Hospital, Dundee DD1 9SY, UK

3–9 December 1989
Breast Cancer: New Developments in Biology, Diagnosis and Treatment
UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr Joseph W. C Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

20–21 January 1989
Hong Kong Surgical Forum
Hong Kong
Information. Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

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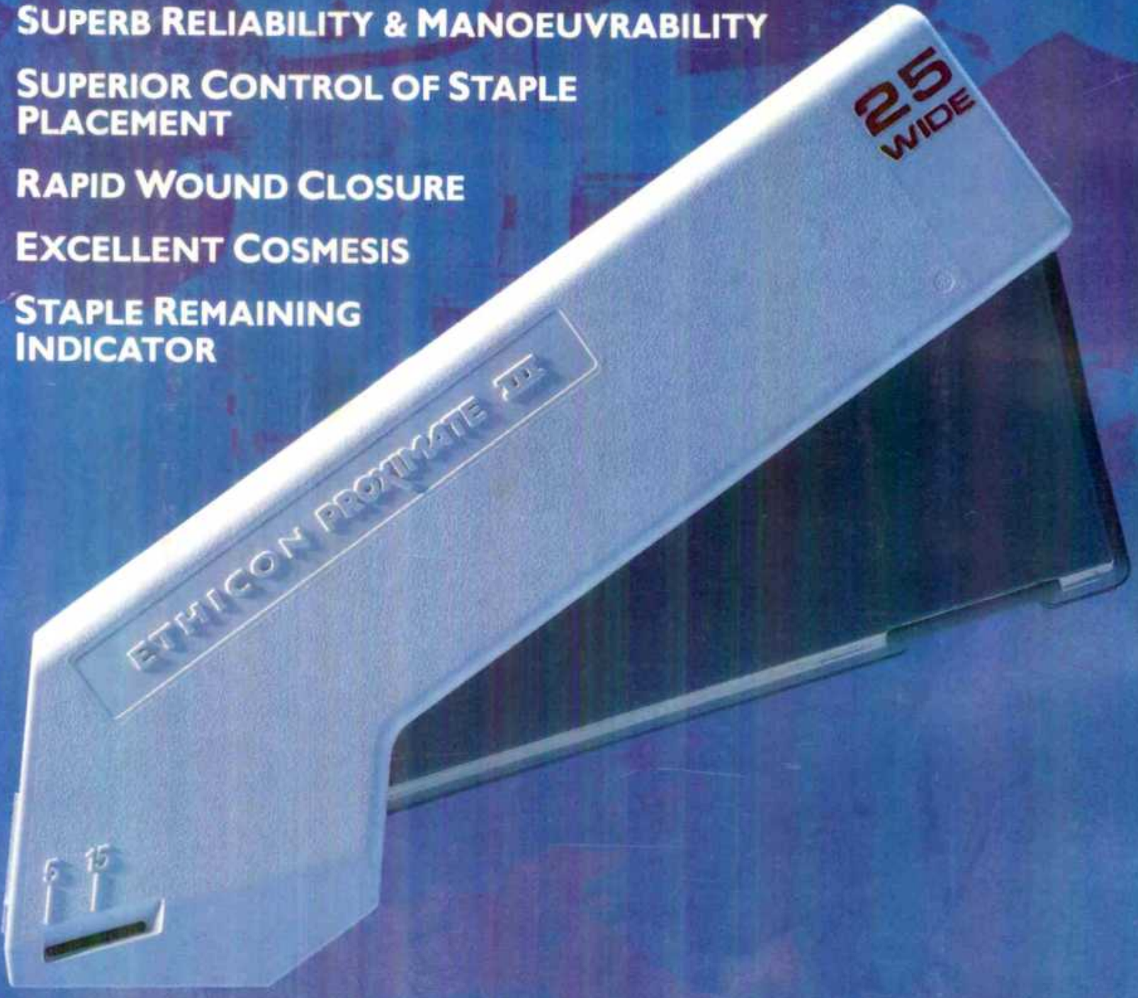

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